3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of selenium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

Selenium is a naturally occurring element that is widely distributed in rocks and soils. Although selenium has been reported at hazardous waste sites where it can occur in many forms, analysis of specific forms present at these sites has not been performed. Selenium has multiple oxidation states (valence states) including -2, 0, +4, and +6. The type of selenium found is a result of its oxidation state which may vary according to ambient conditions, such as pH and microbial activity.

Elemental selenium (selenium[0]) is rarely found naturally, but it is stable in soils. Selenates (selenium[+6]) and selenites (selenium[+4]) are water soluble and can be found in water. Sodium selenate is among the most mobile forms of selenium; because of its high solubility and inability to adsorb to soil particles. More insoluble forms, such as elemental selenium, are less mobile; therefore, there is less risk for exposure. Because of greater bioavailability, water-soluble selenium compounds are probably more lethal than elemental selenium by any route. Selenium is found in nature complexed with multiple compounds, and although various forms are discussed in the profile, many others exist. Plants can contain organic selenium in the form of the amino acids selenomethionine and selenocysteine, along with the dimethyl selenides. Elemental selenium can be oxidized to form selenium dioxide. While the products of oxidation might be expected at the soil surface, elemental selenium would be the expected predominant form in deep soils where anaerobic conditions exist. Selenium sulfides, used in some anti-dandruff shampoos, are not very water soluble and, therefore, like elemental selenium are relatively immobile in the environment.

Much of the selenium released to the environment comes from the burning of coal and other fossil fuels, and from other industrial processes such as the production of rubber. For more information on the

physical and chemical properties of selenium, see Chapter 4. For more information on the potential for human exposure, see Chapter 6.

In humans and animals, selenium is an essential nutrient that plays a role in protecting tissues from oxidative damage as a component of glutathione peroxidase. It is also found in the deiodinases, including type I and II iodothyronine 5'-deiodinase, which convert thyroxine to triiodothyronine and in thioredoxin reductase, which catalyses the NADPH-dependent reduction of the redox protein thioredoxin. The biologically active form of selenium in these enzymes is the modified amino acid, selenocysteine. Humans and animals can be exposed to excessive amounts of selenium through the use of dietary supplements containing selenium. The nutritional role of selenium is further discussed in Section 3.4. Although selenium is an essential nutrient, exposure to high levels via inhalation or ingestion may cause adverse health effects. The mechanism by which selenium exerts toxic effects is unknown, but existing theories are discussed in Section 3.5. Most of the studies available on health effects involve exposure to selenite, selenate, and the organic chemical selenomethionine.

Several factors should be considered when evaluating the toxicity of selenium compounds. The purity and grade of the particular test substance used in the testing are important factors. For example, in studies of selenium sulfide compounds, the amounts of mono- and disulfides are often not specified by the study authors. The solubility and the particle size of selenium compounds also influence their toxicity.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction

or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for selenium. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic

bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

Table 3-1 and Figure 3-1 describe the health effects observed in experimental animals that inhaled elemental selenium dust or hydrogen selenide. Studies using other forms of selenium were not used in the LSE tables and figures (Table 3-1 and Figure 3-1) because either the reporting of the studies was incomplete or no studies on other forms were located. All doses are expressed in terms of total selenium.

3.2.1.1 Death

No studies were located regarding death in humans after inhalation of elemental selenium or selenium compounds.

In animals, the acute lethality of hydrogen selenide and elemental selenium dust when inhaled has been investigated. In guinea pigs exposed to hydrogen selenide for 2, 4, or 8 hours, 5/16 died within 10 days of exposure at 12 mg selenium/m^3, 3/16 died at 6 mg selenium/m^3, and 8/16 died at 6 mg selenium/m^3, respectively (Dudley and Miller 1941).

No deaths were observed among rabbits or guinea pigs exposed to elemental selenium dust at levels of 31 mg selenium/m^3 for 4 hours every other day for 8 exposure days (Hall et al. 1951). Higher levels were not tested.

All LOAEL values from each reliable study for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Table 3-1. Levels of Significant Exposure to Selenium - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Gn Pig (NS)	4 hr				6 (3/16 died)	Dudley and Miller 1941 hydrogen selenide
2	Gn Pig (NS)	8 hr				1 (8/16 died)	Dudley and Miller 1941 hydrogen selenide
3	Gn Pig (NS)	2 hr				12 (8/16 died)	Dudley and Miller 1941 hydrogen selenide
Systemic							
4	Rat (NS)	8 hr	Resp			33 F (pulmonary hemorrhage, pneumonitis)	Hall et al. 1951 elemental
			Hepatic		33 F (congestion; mild central atrophy)		
			Renal	33 F			
			Endocr	33 F			
			Bd Wt	33 F			
5	Gn Pig (NS)	4 hr	Resp			8 (pneumonitis)	Dudley and Miller 1941 hydrogen selenide
			Cardio	8			
			Hepatic		8 (fatty metamorphosis, increased liver weight)		
			Renal	8			
			Endocr	8			

Table 3-1. Levels of Significant Exposure to Selenium - Inhalation (continued)

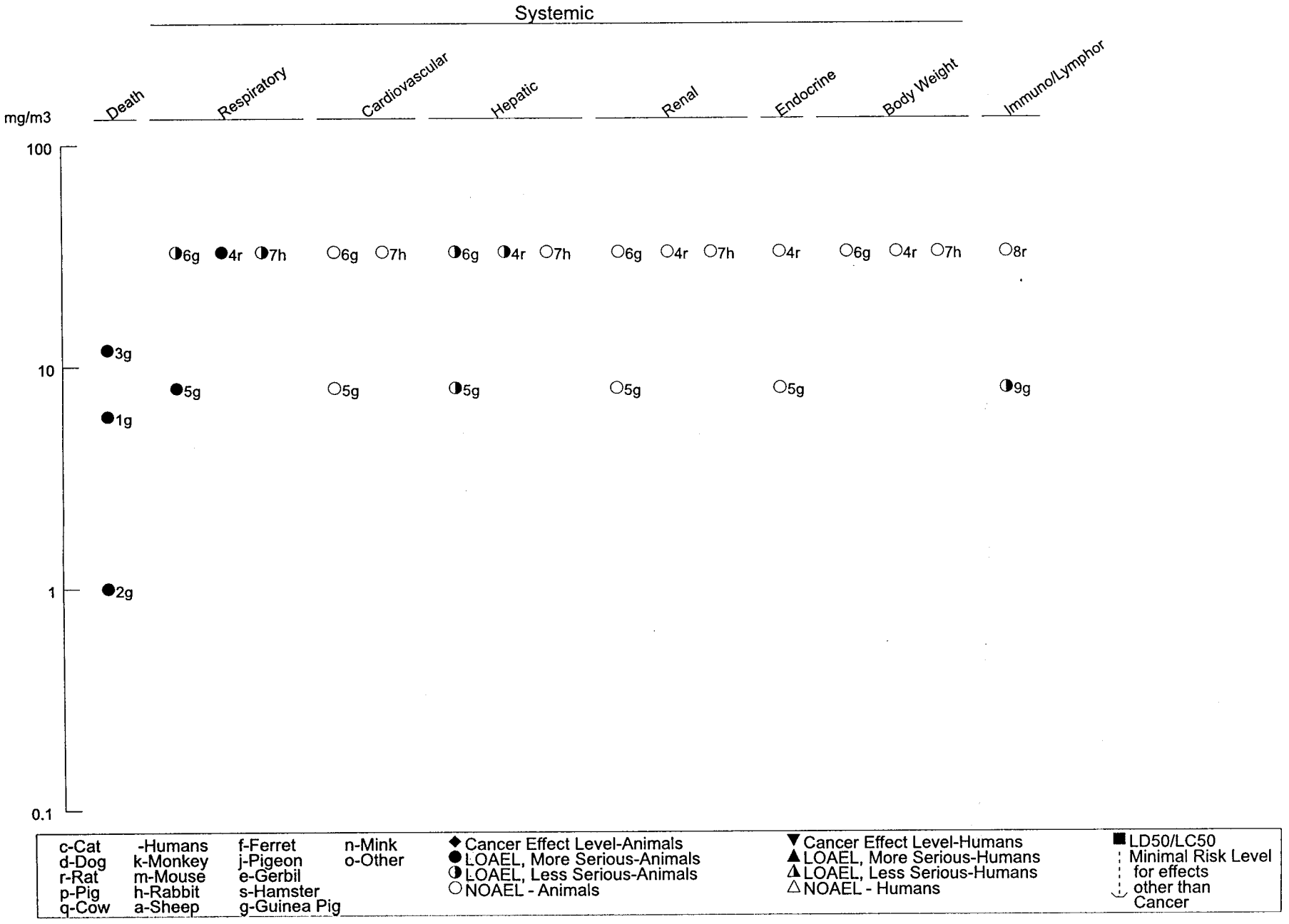
Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
6	Gn Pig (NS)	8 d 4hr/2d	Resp		33 M (mild congestion; mild to moderate interstitial pneumonitis; slight emphysema)		Hall et al. 1951 elemental
			Cardio	33 M			
			Hepatic		33 M (congestion; central atrophy; fatty metamorphosis)		
			Renal	33 M			
			Bd Wt	33 M			
7	Rabbit (NS)	8 d 4hr/2d	Resp		33 F (congestion, mild pneumonitis)		Hall et al. 1951 elemental
			Cardio	33 F			
			Hepatic	33 F			
			Renal	33 F			
			Bd Wt	33 F			
Immunological/Lymphoreticular							
8	Rat (NS)	8 hr		33			Hall et al. 1951 elemental
9	Gn Pig (NS)	4 hr			8 (splenic hyperplasia)		Dudley and Miller 1941 hydrogen selenide

[a]The number corresponds to entries in Figure 3-1.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); (F) = feed; Endocr = endocrine; F = female; gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; (NS) = not specified; Resp = respiratory

Figure 3-1. Levels of Significant Exposure to Selenium - Inhalation

Acute (≤14 days)



3.2.1.2 Systemic Effects

The selenium compounds that are most likely to be encountered in air in occupational settings are dusts of elemental selenium, hydrogen selenide, and selenium dioxide. Other volatile selenium compounds (e.g., dimethyl selenide, dimethyl diselenide) might be encountered in some naturally occurring situations. Because selenium is converted from one form to another, as in plant biosynthesis of selenoamino acids, it is not clear which specific forms may be encountered at hazardous waste sites. If a hazardous waste site specifically contains deposits of compounds of selenium, those compounds could be released off-site in dust or air. Toxicity data for exposures via inhalation are available for elemental selenium, selenium dioxide, selenium oxychloride, hydrogen selenide, and dimethyl selenide. Because there are few studies of inhalation of selenium of any single form, all available studies of inhalation exposures to selenium compounds will be included in this discussion.

In studies of human occupational exposures, it appears that the respiratory tract is the primary site of injury after inhalation of selenium dust or selenium compounds, but gastrointestinal (possibly due to swallowed selenium) and cardiovascular effects, as well as irritation of the skin and eyes, also occur. Little of the available information for humans, however, relates health effects exclusively to measured concentrations of the selenium dust or compounds because of the possibility of concurrent exposures to multiple substances in the workplace. In animals, the respiratory tract is also the primary site of injury following inhalation exposure to selenium dust and hydrogen selenide. Hematological and hepatic effects have also been noted in animals. Inhalation data from laboratory animal studies are available only for acute exposures.

No information was located regarding hematological, musculoskeletal, dermal, or ocular effects in humans or laboratory animals after inhalation exposure to selenium or selenium compounds. The systemic effects that have been observed after inhalation exposure are discussed below. The highest NOAEL values and all LOAEL values for each reliable study for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. In humans, the respiratory system is the primary site of injury after inhalation of elemental selenium or selenium compounds. The largest number of reported human exposures occurred in occupational settings, especially in industries that extract, mine, treat, or process selenium-bearing minerals and in industries that use selenium or selenium compounds in manufacturing. The reports of occupational exposure do not link observed symptoms to specific air concentrations of

elemental selenium or selenium compounds. Several reports, however, have noted common effects associated with inhalation exposure in occupational settings.

Selenium dioxide is formed when selenium is heated in air. Direct exposure to selenium dioxide is, therefore, primarily an occupational hazard and not likely to be a risk at hazardous waste sites. Selenium dioxide forms selenious acid on contact with water, including perspiration, and can cause severe irritation. Acute inhalation of large quantities of selenium dioxide powder can produce pulmonary edema as a result of the local irritant effect on alveoli (Glover 1970). Bronchial spasms, symptoms of asphyxiation, and persistent bronchitis have been noted in workers briefly exposed to high concentrations of selenium dioxide (Wilson 1962). Kinnigkeit (1962) reported that selenium dioxide concentrations of 0.007–0.05 mg selenium/m^3 in a selenium rectifier plant produced slight tracheobronchitis in 9 of 62 exposed workers.

Hydrogen selenide, a highly poisonous selenium compound, is a gas at room temperature, with a density much higher than air. Selenium oxychloride, also highly toxic, is more irritating and corrosive to the human respiratory tract than are other forms of selenium because the compound hydrolyzes to hydrogen chloride (HCl), which can then form hydrochloric acid in humid air and in the respiratory tract (Dudley 1938). Hydrogen selenide and selenium oxychloride are occupational exposure hazards that are not expected to be much of a concern at hazardous waste sites.

Acute inhalation exposure to elemental selenium dust, possibly including some selenium dioxide, in occupational settings has been shown to irritate mucous membranes in the nose and throat and produce coughing, nosebleed, loss of olfaction, and in heavily exposed workers, dyspnea, bronchial spasms, bronchitis, and chemical pneumonia (Clinton 1947; Hamilton 1949). Chronic exposure of 40 workers at a copper refinery produced increased nose irritation and sputum (Holness et al. 1989). The exact concentration of selenium was not given, but the concentration was reported to exceed 0.2 mg selenium/m^3. Confounding variables in this study include concurrent exposure to several other metals including copper, nickel, silver, lead, arsenic, and tellurium.

In experimental animals, the respiratory tract is the primary site of injury following acute inhalation exposure to elemental selenium and selenium compounds. Rats exposed to selenium fumes (selenium concentration and particle size were not reported) for 2–16 minutes experienced moderate to severe respiratory effects, including hemorrhage and edema of the lungs (Hall et al. 1951). Rats exposed to selenium dust (average particle diameter, 1.2 µm) at levels of 33 mg selenium/m^3 for 8 hours experienced

severe respiratory effects, including hemorrhage and edema of the lungs, and several animals died (Hall et al. 1951). Histopathological examinations of surviving animals revealed chronic interstitial pneumonitis. Acute exposure of rabbits and guinea pigs to selenium dust (average particle diameter, 1.2 μm) at a concentration of 33 mg selenium/m^3 resulted in mild interstitial pneumonitis or congestion, and slight emphysema in both species (Hall et al. 1951). Other histological findings included vascular lymphocytic infiltration and intra-alveolar foci of large macrophages.

Acute inhalation exposure of guinea pigs to 8 mg selenium/m^3 as hydrogen selenide for 4 hours, produced diffuse bronchopneumonia and pneumonitis (Dudley and Miller 1941). The investigators do not indicate if any of these guinea pigs died as a result of the exposure. Histologic examination of animals that had died following exposure to higher concentrations revealed thickening of the alveolar walls and congestion of alveolar capillaries (Dudley and Miller 1937). In contrast, 1-hour exposure of rats to 25,958 mg selenium/m^3 as dimethyl selenide produced only minor effects (increased weight of lung and liver) 1 day postexposure. These changes disappeared by 7 days postexposure (Al-Bayati et al. 1992). Enzymatic methylation of selenium compounds is the primary route of detoxification and may explain the low toxicity of dimethyl selenide (Al-Bayati et al. 1992). Although this form of selenium is environmentally relevant since it is formed in soil, plants, and microorganisms, dimethyl selenide appears to be relatively nontoxic in comparison to occupational exposure to hydrogen selenide.

The effects of intratracheal instillation of selenium on pulmonary function may be dependent on the form in which it is supplied (Nonavinakere et al. 1999). Instillation of 0.06 mg selenium/100 g body weight as selenium dioxide produced a significant decrease in respiratory rate and a significant increase in lung resistance compared with controls. Instillation with 0.06 mg selenium/110 g body weight as seleno-L-methionine also produced a decrease in respiratory rate and an increase in lung resistance, but the values were not significantly different from controls.

Intratracheal instillation of 0.3 mg selenium as sodium selenite in male Hartley-guinea pigs decreased dynamic-lung-compliance and increased pulmonary resistance compared with control animals instilled with saline (Bell et al. 1997). Analysis of bronchoalveolar-lavage fluid showed increased activities of lactate dehydrogenase, β-glucuronidase, alkaline phosphatase, and protein, suggesting damage to lung tissue.

Histological analysis of guinea pigs that received single intratracheal instillations of 0.3 mg selenium as sodium selenite found mild acute inflammation in approximately one-third of the lung tissue and a

noticeable amount of sloughed epithelium and mucus within the bronchi (Bell et al. 2000). Lungs of animals treated with 0.06 mg selenium showed neutrophils aggregated in the alveoli and some dilation of the alveoli suggestive of emphysema. Relative lung weights and the ratio of wet/dry lung weight were increased in the selenium-treated animals compared with controls; the increase was only significant for those receiving the higher dose of selenium. Leucocyte counts in bronchoalveolar-lavage fluid were decreased for selenium-treated animals compared with controls, and the difference was significant for the animals receiving 0.3 mg selenium, but not the 0.06 mg dosage.

No studies were located regarding respiratory effects in animals after intermediate or chronic inhalation of selenium or selenium compounds.

Cardiovascular Effects. Several workers experienced symptoms of shock, including lower blood pressure and elevated pulse rates, following an acute exposure (at most 20 minutes) to selenium dioxide fumes resulting from a fire (Wilson 1962). The subjects were treated with oxygen and inhalation of ammonia vapor, and pulse rates were normalized within 3 hours.

Cardiovascular effects were not observed in guinea pigs exposed to hydrogen selenide at 8 mg selenium/m^3 for 4 hours (Dudley and Miller 1941), or in guinea pigs and rabbits exposed to elemental selenium dust (average particle diameter, 1.2 μm) every other day at 33 mg selenium/m^3 for eight 4-hour exposure periods (Hall et al. 1951).

Gastrointestinal Effects. Vomiting and nausea were reported in workers exposed to high concentrations of selenium dioxide for a maximum of 20 minutes during a fire (Wilson 1962). Stomach pain was frequently reported by workers exposed to elemental selenium and selenium dioxide at a selenium rectifier plant (Glover 1967), and by copper refinery workers exposed to an unspecified form of selenium (Holness et al. 1989). Exposure concentrations were not reported for the rectifier plant, but were greater than 0.2 mg selenium/m^3 at the copper refinery.

No studies were located regarding gastrointestinal effects in animals after inhalation of selenium or selenium compounds.

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation of selenium or selenium compounds.

Hepatoxicity has been observed in experimental animals following inhalation exposure to elemental selenium dust and to hydrogen selenide. One month after an 8-hour exposure to elemental selenium dust at a level of 33 mg selenium/m^3, most rats exhibited slight liver congestion, and a few exhibited mild centrilobular atrophy (Hall et al. 1951). In contrast, 1 week after exposure to 25,958 mg selenium/m^3 as dimethyl selenide for 1 hour, rats showed no observable changes in the liver (Al-Bayati et al. 1992). Three weeks following acute exposure to elemental selenium dust at a level of 33 mg selenium/m^3 for 4 hours every other day for 8 days, 4/10 guinea pigs exhibited slight hepatic congestion with mild central atrophy, and 2/10 showed some fatty hepatocellular degeneration (Dudley and Miller 1941). In contrast, exposure of guinea pigs to lower concentrations of selenium (8 mg/m^3), as hydrogen selenide, for a single 4-hour period produced mild fatty hepatocellular metamorphosis (Dudley and Miller 1941).

Renal Effects. No studies were located regarding renal effects in humans after inhalation of selenium or selenium compounds.

The kidneys do not appear to be affected in guinea pigs (Dudley and Miller 1941; Hall et al. 1951) after acute inhalation exposure to 33 mg selenium/m^3 as hydrogen selenide for 8 hours or to 8 mg selenium/m^3 as elemental selenium dust for 4 hours. Likewise, the kidneys were not affected in rabbits following acute inhalation exposure to 33 mg selenium/m^3 as hydrogen selenide for 8 hours (Hall et al. 1951) or in rats following acute inhalation exposure to 25,958 mg selenium/m^3 as dimethyl selenide for 1 hour or to 33 mg selenium/m^3 as hydrogen selenide for 8 hours (Al-Bayati et al. 1992; Hall et al. 1951).

Endocrine Effects. No studies were located regarding endocrine effects in humans after inhalation of selenium or selenium compounds.

No histopathological changes in the adrenal gland were observed in guinea pigs exposed to hydrogen selenide at 8 mg selenium/m^3 for 4 hours (Dudley and Miller 1941), or in rats exposed to elemental selenium at 33 mg selenium/m^3 for 8 hours (Hall et al. 1951).

Body Weight Effects. No studies were located regarding effects on body weight in humans following inhalation of selenium or selenium compounds.

No effects on body weight were observed in guinea pigs following a single 8-hour exposure to elemental selenium at 33 mg selenium/m^3, or in guinea pigs and rabbits exposed to elemental selenium dust at 33 mg selenium/m^3 every other day for 4 hours for a total of eight exposures (Hall et al. 1951).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans after inhalation exposure to selenium or selenium compounds.

Lymphoid hyperplasia was noted in the spleen of guinea pigs following a single 4-hour exposure at 8 mg selenium/m^3 as hydrogen selenide (Dudley and Miller 1941). Histopathological changes in the spleen were not observed in guinea pigs exposed to elemental selenium dust (average particle diameter, 1.2 µm) at 33 mg selenium/m^3 for 8 hours (Hall et al. 1951). Injury to the spleen was observed in guinea pigs following exposure for 4 hours, every other day, for 8 days to elemental selenium dust at a level of 33 mg selenium/m^3 (Hall et al. 1951). Specific effects included congestion of the spleen, fissuring red pulp, and increased polymorphonuclear leukocytes (Hall et al. 1951).

3.2.1.4 Neurological Effects

Information concerning possible neurological effects caused by inhalation of selenium or selenium compounds is limited. Severe frontal headaches were reported by workers exposed during an accident to high concentrations of selenium fumes (compound not stated) for approximately 2 minutes (Clinton 1947). Workers at a selenium rectifier plant reported symptoms of malaise and irritability when working with selenium (exposure probably to selenium dioxide and elemental selenium, but form was not stated) (Glover 1967). The symptoms resolved whenever the workers were moved to other work. Urinary concentrations of selenium were about 0.08 mg/L, compared to 0.024–0.034 mg/L in unexposed workers.

No studies were located regarding neurological effects in animals after inhalation of selenium or selenium compounds.

No studies were located regarding the following health effects in humans or animals after inhalation exposure to selenium or selenium compounds:

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

There are no epidemiologic data that support a causal association between the inhalation of elemental selenium dusts or selenium compounds and the induction of cancer in humans (Gerhardsson et al. 1986; Wester et al. 1981). In one study, postmortem samples were collected from copper smelter workers who were exposed to several different airborne compounds, including selenium compounds. Samples from lung cancer cases had lower concentrations of selenium in lung tissue than samples from controls or from workers who had died from other causes (Gerhardsson et al. 1986). In another autopsy study of smelter workers, Wester et al. (1981) found that the selenium concentrations in kidney tissues from workers who had died of malignancies were lower than the selenium concentrations in kidney tissues from workers who died of other causes. Further discussions regarding the cancer protective effects of selenium can be found in Section 3.2.2.7.

No studies were located regarding carcinogenic effects in laboratory animals after inhalation exposure to selenium or selenium compounds.

3.2.2 Oral Exposure

Table 3-2 and Figure 3-2 describe the health effects observed in humans and experimental animals associated with dose and duration of oral exposure to selenium and selenium compounds (i.e., elemental selenium dust, selenium dioxide dissolved in water [selenious acid], sodium selenate, sodium selenite, potassium selenate, and dietary selenium compounds, which include selenoamino acids). All doses for these compounds are expressed in terms of total selenium. Table 3-3 and Figure 3-3 describe health effects observed in laboratory animals following oral exposure to selenium sulfides (SeS_2 and SeS) at varying doses and exposure durations. All doses for selenium sulfide compounds are expressed in terms of the compound, because selenium sulfide preparations often exist as a variable mixture of the mono- and disulfide forms, precluding accurate expression of the dose in terms of total selenium.

Table 3-2. Levels of Significant Exposure to Selenium - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	ACUTE EXPOSURE						
	Death						
1	Rat (Sprague-Dawley)	once (G)				6700 M (LD_{50})	Cummins and Kimura 1971 elemental
2	Rat (Sprague-Dawley)	once (GW)				7 M (LD_{50})	Cummins and Kimura 1971 selenite
3	Rat (Sprague-Dawley)	14 d ad lib (W)				0.418 F (7/12 died)	NTP 1996 sodium selenate
4	Rat (NS)	once (G)				4.8 F (LD_{50})	Pletnikova 1970 selenite
5	Rat (Wistar)	once (GW)				48 (LD_{50})	Singh and Junnarkar 1991 selenium dioxide
6	Mouse (NS)	once (G)				3.2 M (LD_{50})	Pletnikova 1970 selenite
7	Mouse (ICR)	once (G)				35.9 M (LD_{50})	Sayato et al. 1993 D,L-selenocystine
8	Mouse (Swiss)	once (GW)				16 M (LD_{50})	Singh and Junnarkar 1991 selenium dioxide
9	Gn Pig (NS)	once (G)				2.3 F (LD_{50})	Pletnikova 1970 selenite

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
10	Rabbit (NS)	once (G)				1.0 F (LD_{50})	Pletnikova 1970 selenite
	Systemic						
11	Rat (Sprague-Dawley)	14 d ad lib (W)	Bd Wt	0.251 F		0.418 F (significant (36%) reduction in body weight)	NTP 1996 sodium selenate
12	Mouse (BALB/c)	14 d ad lib (W)	Hemato	0.38 M	0.82 M (significant increase in red blood cell count)		Johnson et al. 2000 Selenite
			Hepatic	0.38 M	0.82 M (significant decrease in relative liver weight)		
			Renal	0.17 M	0.38 M (significant increase in relative kidney weight)		
			Bd Wt	0.38 M	0.82 (significant decrease in body weight gain)		
13	Mouse (BALB/c)	14 d ad lib (W)	Hemato	1.36 M			Johnson et al. 2000 selenomethionine
			Hepatic	1.36 M			
			Renal	1.36 M			
			Bd Wt	1.36 M			
14	Pig (NS)	5 d	Resp	1.25			Panter et al. 1996 organic
			Cardio	1.25			
			Hepatic	1.25			
			Renal	1.25			
			Dermal	1.25			
			Bd Wt			1.25 (5% loss of body weight)	

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
Immunological/Lymphoreticular							
15	Mouse (BALB/c)	14 d ad lib (W)		0.38 M	0.82 M (increased proliferation of splenic lymphocytes and LPS-induced production of TNF alpha and IL-1beta)		Johnson et al. 2000 Selenite
16	Mouse (BALB/c)	14 d ad lib (W)		1.36 M			Johnson et al. 2000 selenomethionine
Neurological							
17	Mouse (Swiss)	once (GW)			1.6 (decreased activity, muscle tone, touch response, respiration; hypothermia)		Singh and Junnarkar 1991 selenium dioxide
18	Mouse (BALB/c)	14 d ad lib (W)		0.24 M	0.58 M (significant increase in the levels of striatal dihydroxyphenylacetic acid and homovanillic acid)		Tsunoda et al. 2000 Selenite
19	Mouse (BALB/c)	14 d ad lib (W)		1.96 M			Tsunoda et al. 2000 Organic selenium
20	Pig (NS)	10 d 1x/d (C)				1.3 (hypoactivity, focal symmetrical poliomalacia, histopathological lesions in brain and spinal cord)	Wilson et al. 1989 selenite

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL: Less Serious (mg/kg/day)	LOAEL: Serious (mg/kg/day)	Reference Chemical Form
Developmental							
21	Hamster (Syrian LKV)	once Gd 8 (GW)		7.1		7.9 (encephalocele; decreased crown-rump length)	Ferm et al. 1990 selenite
22	Hamster (Syrian LKV)	once Gd 8 (GW)				7.1 (encephalocele)	Ferm et al. 1990 selenate
23	Hamster (Syrian LKV)	once Gd 8 (GW)			5.9 (decreased fetal crown-rump length)		Ferm et al. 1990 selenomethionine

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	INTERMEDIATE EXPOSURE						
	Death						
24	Rat (Sprague-Dawley)	6 wk ad lib (F)				0.48 M (1/8 died)	Halverson et al. 1966 selenite
25	Rat (Sprague-Dawley)	6 wk ad lib (F)				0.4 M (1/8 died)	Halverson et al. 1966 organic
26	Rat (Fischer- 344)	13 wk (W)				2.54 (20/20 died)	NTP 1994 selenate
27	Rat (Fischer- 344)	13 wk (W)				1.67 F (2/10 died)	NTP 1994 selenite
28	Rat (Sprague-Dawley)	4-6 wk ad lib (W)				0.84 M (4/6 died)	Palmer and Olson 1974 selenite
29	Rat (Sprague-Dawley)	4-6 wk ad lib (W)				0.84 M (2/6 died)	Palmer and Olson 1974 selenate
30	Rat (Wistar)	1 yr daily ad lib (W)				1.05 F (3/5 died) 1.05 M (1/3 died)	Rosenfeld and Beath 1954 selenate

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
31	Rat (BLU:[LE])	365 d (W)				0.28 (50% males died at 58 days 50% females died at 160 days)	Schroeder and Mitchener 1971a selenite
32	Mouse (ICR)	30 d 6d/wk (G)				14.2 M (15/15 died)	Sayato et al. 1993 D,L-selenocystine
	Systemic						
33	Human	20 wk (IN)	Endocr	0.001			Duffield et al. 1999
34	Human	120 d (F)	Endocr		0.0048 M (significant increase in thyroid stimulating hormone)		Hawkes and Keim 1995 NS
35	Monkey (Macaca fascicularis)	gd 20-50 1x/d (GW)	Gastro	0.025 F	0.15 F (vomiting)		Tarantal et al. 1991 selenomethionine
			Bd Wt	0.025 F	0.15 F (increased weight loss)		
36	Rat (Wistar)	110 d ad lib (F)	Endocr	0.105 M	0.105 M (significant reduction in type I deiodinase activity)		Behne et al. 1992 sodium selenite
			Bd Wt	0.105 M			
37	Rat (Wistar)	110 d ad lib (F)	Endocr		0.118 M (significant reduction in type I deiodinase activity)		Behne et al. 1992 selenomethionine
			Bd Wt		0.118 M (significant reduction in body weight (15%))		

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
38	Rat (Sprague-Dawley)	2 mo ad lib (F)	Hepatic	0.1 M	0.2 M (nodular regenerative hyperplasia, increased relative liver weight)		Bioulac-Sage et al. 1992 selenite
			Bd Wt	0.2 M			
39	Rat (Sprague-Dawley)	8 wk (F)	Resp	0.45 M			Chen et al. 1993 selenite
			Cardio	0.45 M			
			Gastro	0.45 M			
			Hepatic		0.45 M (diffuse panlobular vacuolar accumulation of glycogen and lipid)		
			Renal	0.45 M			
			Bd Wt		0.25 M (final body weights about 14% lower than controls)	0.35 M (final body weights about 29% lower than controls)	
40	Rat (Sprague-Dawley)	40 d ad lib (F)	Hemato	0.27 M			Eder et al. 1995 sodium selenite
			Endocr	0.026 M	0.055 M (significant reduction in serum tri-iodothyronine levels)		
			Bd Wt	0.27 M			

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
41	Rat (Sprague-Dawley)	6 wk ad lib (F)	Hemato	0.24 M	0.32 M (23% decrease in hemoglobin)	0.56 M (79% decrease in hemoglobin)	Halverson et al. 1966 organic
			Hepatic		0.4 M (6-fold increase in bilirubin)		
			Endocr	0.32 M	0.4 M (pancreas weight 1.4 times greater than diet restricted controls)		
			Bd Wt	0.32		0.4 M (body weight gain 36% lower than controls)	
42	Rat (Sprague-Dawley)	6 wk ad lib (F)	Endocr		0.09 M (significant increase in serum TSH (~30%))		Hotz et al. 1997 sodium selenate
			Bd Wt	0.09 M			
			Metab		0.09 M (significant increase in GSH-Px in kidney (~30%) and erythrocytes (~100%))		
43	Rat (Wistar)	3 mo 1x/d (F)	Hepatic		0.002 M (sporadic infiltrations of mononuclear cells in portal canals and weak activation of Kupffer cells)	0.005 M (distict swelling of Kupffer cells in dilated sinusoidal vessels and necrotic areas comprising single groups of hepatocytes)	Kolodziejczyk et al. 2000 sodium selenite

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
44	Rat (Fischer- 344)	13 wk (W)	Resp	1.57 M			NTP 1994 selenate
			Cardio	1.57 M			
			Gastro	1.57 M			
			Hemato	0.92 M	1.57 M (increased hematocrit and hemoglobin associated with decreased water intake)		
			Musc/skel	1.57 M			
			Hepatic	0.92 M	1.57 M (increased bile acids indicating cholestasis)		
			Renal	0.31 F	0.47 F (minimal papilla degeneration of the kidneys)		
			Endocr	1.57 M			
			Ocular	1.57 M			
			Bd Wt	0.47 F	0.88 F (body weights 10% less than controls)	1.35 F (body weights 29% less than controls, associated with decreased water intake)	

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
45	Rat (Fischer- 344)	13 wk (W)	Resp	1.67 F			NTP 1994 selenite
			Cardio	1.67 F			
			Gastro	1.67 F			
			Hemato	0.86 F	1.67 F (increased hematocrit associated with decreased water intake)		
			Musc/skel	1.67 F			
			Hepatic	1.67 F			
			Renal	0.28 F	0.5 F (mild papilla degeneration)		
			Endocr	1.67 F			
			Ocular	1.67 F			
			Bd Wt	0.98 M		1.59 M (body weights 34% less than controls; associated with decreased water intake)	
46	Rat (Sprague-Dawley)	23-29 d ad lib (W)	Bd Wt	0.167[b] M 0.209 F	0.293[b] M 0.334 F (significant (11%) reduction in body weight)	0.418 (significant (20% male, 39% female) reduction in body weight)	NTP 1996 sodium selenate
47	Rat (Sprague-Dawley)	4-6 wk ad lib (W)	Hepatic			0.84 M (cirrhosis)	Palmer and Olson 1974 selenate
			Bd Wt		0.42 M (body weight gain 10% lower than controls)		
48	Rat (Sprague-Dawley)	6 wk ad lib (F)	Bd Wt	0.125 M			Salbe and Levander 1990a selenate

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
49	Rat (Sprague-Dawley)	6 wk ad lib (F)	Bd Wt	0.125 M			Salbe and Levander 1990a selenomethionine
50	Rat (Wistar)	3-6 wks ad lib (W)	Endocr		0.64 F (decreased somatomedin C)		Thorlacius-Ussing 1990 selenite
			Bd Wt			0.64 F (body weight gain 30% lower than controls)	
51	Rat (Wistar)	12-14 wk ad lib	Cardio			0.324 (degeneration of heart tissue with disruption of myofibrils and sarcomeres)	Turan et al. 1999a sodium selenite
			Hepatic			0.324 (degeneration of liver tissue with dilation of sinusoidal capillaries)	
			Bd Wt		0.324 (significant decrease in body weight (17%))		
52	Mouse (ICR)	90 d (G)	Hepatic	2.4 M	4.7 M (increased serum aspartate aminotransferase and alanine aminotransferase)		Hasegawa et al. 1994 D,L-selenocystine
			Bd Wt	2.4 M	4.7 M (body weights 16% lower than controls)	7.1 M (body weights 22% lower than controls)	

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
53	Mouse (B6C3F1)	13 wk (W)	Resp	7.17 F			NTP 1994 selenate
			Cardio	7.17 F			
			Gastro	7.17 F			
			Hemato	7.17 F			
			Musc/skel	7.17 F			
			Hepatic	7.17 F			
			Renal	1.07 M	1.87 M (increased kidney weight associated with decreased water intake)		
			Endocr	7.17 F			
			Ocular	7.17 F			
			Bd Wt	1.87	2.95 M (body weights 13% lower than controls; decreased water intake)	5.45 M (body weights 24% lower than controls; decreased water intake)	

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
54	Mouse (B6C3F1)	13 wk (W)	Resp	3.83 F			NTP 1994 selenite
			Cardio	3.83 F			
			Gastro	3.83 F			
			Hemato	3.83 F			
			Musc/skel	3.83 F			
			Hepatic	3.83 F			
			Renal	0.91 M	1.61 M (increased relative kidney weight; decreased water intake)		
			Endocr	3.83 F			
			Ocular	3.83 F			
			Bd Wt	1.61 M		3.31 M (body weights 20% lower than controls; decreased water intake)	
55	Mouse (ICR)	30 d 6d/wk (G)	Hepatic	4.7 M	9.4 M (significant 2-3-fold increases in aspartate aminotransferase and alanine aminotransferase)		Sayato et al. 1993 D,L-selenocystine
			Renal	9.4 M			
			Bd Wt		9.4 M (final body weight about 13% lower than controls)	18.9 M (final body weight about 29% lower than controls)	
56	Mouse Balby	12 wk ad lib (F)	Hepatic		0.2 M (vacuolization of hepatocytes)		Skowerski et al. 1997a sodium selenite

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
57	Mouse Balby	12 wk ad lib (F)	Cardio		0.2 M (cardiocytes have numerous damaged mitochondria, large number of lipid droplets and numerous lysosomes)		Skowerski et al. 1997b sodium selenite
			Bd Wt	0.2 M			
58	Rabbit (New Zealand)	3 mo ad lib (F)	Cardio			0.137 (disruption of myofibrils, irregular sarcomeres, and diosrganization of bands in sarcomeres)	Turan et al. 1999b sodium selenite
			Hemato	0.137			
			Bd Wt	0.137			
59	Pig (mixed breed)	8 wk ad lib (F)	Hepatic		1.1 (vacuolar degeneration, portal fibrosis)		Baker et al. 1989 selenate
			Dermal		1.1 (cracked hoof walls)		
			Bd Wt			1.1 (body weight gain 83% lower than controls, accompanied by decreased food intake)	
60	Pig (NS)	35 d ad lib (F)	Dermal	0.014	0.25 (hoof cracking)		Mahan and Magee 1991 selenite
			Bd Wt	0.25		0.47 (body weight gain 78% lower than controls, accompanied by decreased food intake)	

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
61	Pig (crossbred L x Y)	8 wk ad lib (F)	Hepatic	0.33		0.59 (atrophic cirrhosis)	Mihailovic et al. 1992 selenite
			Dermal	0.33	0.59 (hoof cracking, alopecia, redness of skin, petechiae)		
62	Pig (NS)	31 +/- 14 d	Cardio	1.25			Panter et al. 1996 D,L-selenomethionine
			Hepatic	1.25			
			Renal	1.25			
			Dermal		1.25 (symmetrical hair loss, dry scaling skin, cracked overgrown hooves 3/5 pigs)		
			Bd Wt		1.25 (body weight gain 15% less than controls)		
63	Pig (NS)	16 +/- 16 d	Resp	1.25			Panter et al. 1996 selenate
			Cardio	1.25			
			Hepatic	1.25			
			Renal	1.25			
			Dermal		1.25 (symmetrical hair loss, dry scaling skin, cracked overgrown hooves 1/5 pigs)		
			Bd Wt			1.25 (body weight gain 22% less than controls)	

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
64	Pig (NS)	34 d ad lib (F)	Cardio			0.46 (vacuolation, pyknosis of nuclei)	Stowe et al. 1992 NS
			Musc/skel			0.46 (hyperplasia of sarcolemma nuclei; disintegration of myofibrils)	
65	Pig (Duroc)	NS ad lib (F)	Dermal		0.4 F (2/10 alopecia; 1/10 hoof separation)		Wahlstrom and Olson 1959b selenite
			Bd Wt	0.4 F			
66	Cattle Hereford	120 d 1x/d (F)	Resp	0.808 M			O'Toole and Raisbeck 1995 selenomethionine
			Cardio	0.808 M			
			Gastro	0.808 M			
			Musc/skel	0.808 M			
			Hepatic	0.808 M			
			Renal	0.808 M			
			Endocr	0.808 M			
			Dermal	0.158 M	0.288 M (mild parakeratosis of hoof)	0.808 M (severe parakeratosis and epithelial hyperplasia of hoof)	
			Ocular	0.808 M			

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
67	Cattle Hereford	120 d 1x/d (F)	Resp	0.808 M			O'Toole and Raisbeck 1995 sodium selenite
			Cardio	0.808 M			
			Gastro	0.808 M			
			Musc/skel	0.808 M			
			Hepatic	0.808 M			
			Renal	0.808 M			
			Endocr	0.808 M			
			Dermal	0.288 M	0.808 M (mild parakeratosis of hoof)		
			Ocular	0.808 M			
	Immunological/Lymphoreticular						
68	Rat (Sprague-Dawley)	10 wk ad lib (W)			0.7 F (decreased delayed-type hypersensitivity; increased thymus weight)		Koller et al. 1986 selenite
69	Mouse (BALB/c)	47 d ad lib (W)			0.173 N S (reduced B-cell function and OVA-specific antibody concentration)		Raisbeck et al. 1998 selenocystine
70	Mouse (BALB/c)	47 d ad lib (W)			0.173 N S (reduced B-cell function and OVA-specific antibody concentration)		Raisbeck et al. 1998 selenomethionine
71	Mouse (BALB/c)	47 d ad lib (W)			0.173 N S (reduced OVA-specific antibody concentration)		Raisbeck et al. 1998 sodium selenite

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
72	Cattle Hereford	120 d 1x/d (F)		0.808 M				O'Toole and Raisbeck 1995 selenomethionine
73	Cattle Hereford	120 d 1x/d (F)		0.808 M				O'Toole and Raisbeck 1995 sodium selenite
	Neurological							
74	Human	120 d (F)		0.0048 M				Hawkes and Hornbostel 1996 selenomethionine
75	Monkey (Macaca fascicularis)	30 d 1x/d (GW)		0.08	0.12 F (hypothermia)			Cukierski et al. 1989 selenomethionine
76	Pig (mixed breed)	7 wk ad lib (F)				1.3	(tetraplegia, poliomyelomalacia)	Baker et al. 1989 organic
77	Pig (crossbred L x Y)	8 wk ad lib (F)		0.33		0.59	(hind limb paresis, hind limb ataxia, symmetric poliomylomalacia of the ventral horn of the spinal cord)	Mihailovic et al. 1992 selenite
78	Pig (NS)	20-42d ad lib (F)		1		2.1	(poliomylelomalacia, paralysis, difuse gliosis of the spinal cord)	Wilson et al. 1983 selenite

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
79	Cattle Hereford	120 d 1x/d (F)		0.808 M			O'Toole and Raisbeck 1995 selenomethionine
80	Cattle Hereford	120 d 1x/d (F)		0.808 M			O'Toole and Raisbeck 1995 sodium selenite
	Reproductive						
81	Monkey (Macaca fascicularis)	30 d 1x/d (GW)		0.06 F	0.08 F (altered menstrual cycle)		Cukierski et al. 1989 selenomethionine
82	Rat (Wild)	5 wk (F)			0.1 M (3.9% abnormal sperm; decrease in live sperm)	0.2 M (24.6% abnormal sperm; decreased live sperm, and sperm motility; decreased testicular weight)	Kaur and Parshad 1994 selenite
83	Rat (Fischer- 344)	13 wk (W)			0.29[b] M (15% decreased sperm counts) 0.31 F (more time in diestrus and less time in proestrus, estrus, and metestrus than controls)		NTP 1994 selenate
84	Rat (Fischer- 344)	13 wk (W)		0.5 F	0.17[b] M (11% decrease epididymal sperm counts) 0.86 F (more time in diestrus and less time in proestrus and estrus)		NTP 1994 selenite

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
85	Rat (Wistar)	12-14 wk ad lib				0.324 (testicular hypertrophy)	Turan et al. 1999a sodium selenite
86	Mouse (IVCS)	48 d ad lib (W)		0.17 F	0.34 F (proportion of mice with longer estrus cycles increased by 11.8%)		Nobunaga et al. 1979 selenite
87	Mouse (B6C3F1)	13 wk (W)		7.17 F 5.45[b] M			NTP 1994 selenate
88	Mouse (B6C3F1)	13 wk (W)		3.83 F 3.31[b] M			NTP 1994 selenite
89	Rabbit (New Zealand)	6 wks 1x/wk (GW)			0.001 M (significant reduction in serum testosterone (49%))		El-Zarkouny et al. 1999 sodium selenite
90	Pig (Duroc)	NS ad lib (F)				0.4 (decreased fertility, maternal toxicity)	Wahlstrom and Olson 1959b selenite
	Developmental						
91	Rat (Wistar)	8 wks ad lib (W)			0.64 (decrease weight gain of pups exposed during lactation)		Thorlacius-Ussing 1990 selenite
92	Mouse (IVCS)	pre-Gd:30 d Gd 0-18 ad lib (W)		0.17	0.34 (decreased fetal body weight, delayed vertebral ossification)		Nobunaga et al. 1979 selenite

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
93	Pig (Duroc)	NS ad lib (F)				0.4	(increased number of deaths between birth and weaning; reduced birth weight and reduced body weight at weaning)	Wahlstrom and Olson 1959b selenite
94	Cattle	3 mo ad lib (F)		0.265				Yaeger et al. 1998 sodium selenite

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Death						
95	Rat (Wistar)	2 yr ad lib (F)				0.5 (reduced longevity from about 500 days to about 60-100 days)	Harr et al. 1967; Tinsley et al. 1967 selenate, selenite
	Systemic						
96	Human	>3 yr (F)	Endocr	0.006 F	0.007 F (significant reduction in serum levels of triiodothyronine)		Bratter and Negretti De Bratter 1996 NS
97	Human	>2 yr (F)	Hemato	0.0098			Longnecker et al. 1991 organic
			Musc/skel	0.0098			
			Hepatic	0.0098			
			Dermal	0.0098			
98	Human	lifetime (F)	Dermal	0.015[c]	0.023 (selenosis: sloughing of nails and brittle hair)		Yang and Zhou 1994 Organic
99	Human	yr (F)	Cardio	0.025			Yang et al. 1989a organic
			Hemato	0.015	0.016 (increased prothrombin time)		
			Hepatic	0.025			
			Dermal	0.015	0.016 (brittle nails)		

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
100	Rat (Wistar)	2 yr ad lib (F)	Musc/skel	0.10	0.20 (soft bones)		Harr et al. 1967; Tinsley et al. 1967 selenite, selenate
			Hepatic	0.025	0.10 (hyperplastic lesions)		
			Renal	0.025	0.1 (nephritis)		
101	Rat (Osborne-Mendel)	24 mo ad lib (F)	Resp	0.50 F			Nelson et al. 1943 organic
			Gastro	0.50 F			
			Musc/skel	0.50 F			
			Hepatic			0.25 F (slight to moderate cirrhosis)	
			Endocr	0.5 F			
			Dermal	0.5 F			
102	Mouse (Swiss)	lifetime ad lib (W)	Resp			0.57 (amyloidosis)	Schroeder and Mitchener 1972 selenate
			Cardio			0.57 (amyloidosis)	
			Hepatic			0.57 (amyloidosis)	
			Renal			0.57 (amyloidosis)	
			Endocr			0.57 (amyloidosis of adrenal gland)	
			Dermal		0.57 (poor coat)		
			Bd Wt	0.57			

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
103	Mouse (Swiss)	lifetime ad lib (W)	Resp				0.57	(amyloidosis)	Schroeder and Mitchener 1972 selenite
			Cardio				0.57	(amyloidosis)	
			Hepatic				0.57	(amyloidosis)	
			Renal				0.57	(amyloidosis)	
			Endocr				0.57	(amyloidosis of adrenal gland)	
			Dermal		0.57	(poor coat)			
			Bd Wt	0.57					
Neurological									
104	Human	yr (F)		0.027			0.058	(tendon hyperflexia, peripheral anesthesia, pain in extremities, polyneuritis)	Yang et al. 1983 organic
Reproductive									
105	Rat (Wistar)	1 yr daily ad lib (W)		0.21	0.35	(50% reduction in number of pups reared in second generation)	1.05	(decreased fertility, pup survival, maternal toxicity; second generation failed to reproduce)	Rosenfeld and Beath 1954 selenate
106	Mouse (CD)	3 gen ad lib (W)					0.57	(failure to breed in the third generation)	Schroeder and Mitchener 1971b selenate

Table 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
Developmental									
107	Mouse (CD)	3 gen ad lib (W)					0.57	(increased number of runts; postnatal lethality)	Schroeder and Mitchener 1971b selenate

[a]The number corresponds to entries in Figure 3-2.
[b]Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[c]Used to derive a chronic oral minimal risk level (MRL) of 0.005 mg/kg-day; The NOAEL is divided by an uncertainty factor of 3 (for human variability).

ad lib = ab libitum; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = female; (G) = gavage; gastro = gastrointestinal; gd = gestation day; GHS-Px = selenium-dependent glutathione peroxidase; (GW) = gavage in water; Hemato = hematological; (IN) = ingestion; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; LPS = lipopolysaccharide; M = male; metab = metabolic; mg/kg/day = milligram per kilogram per day; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; (NS) = not specified; Resp = respiratory; TNF = tumor necrosis factor; TSH = thyroid-stimulating hormone; (W) = water; wk = week(s); x =time(s); yr = year(s)

Figure 3-2. Levels of Significant Exposure to Selenium - Oral

Acute (≤14 days)

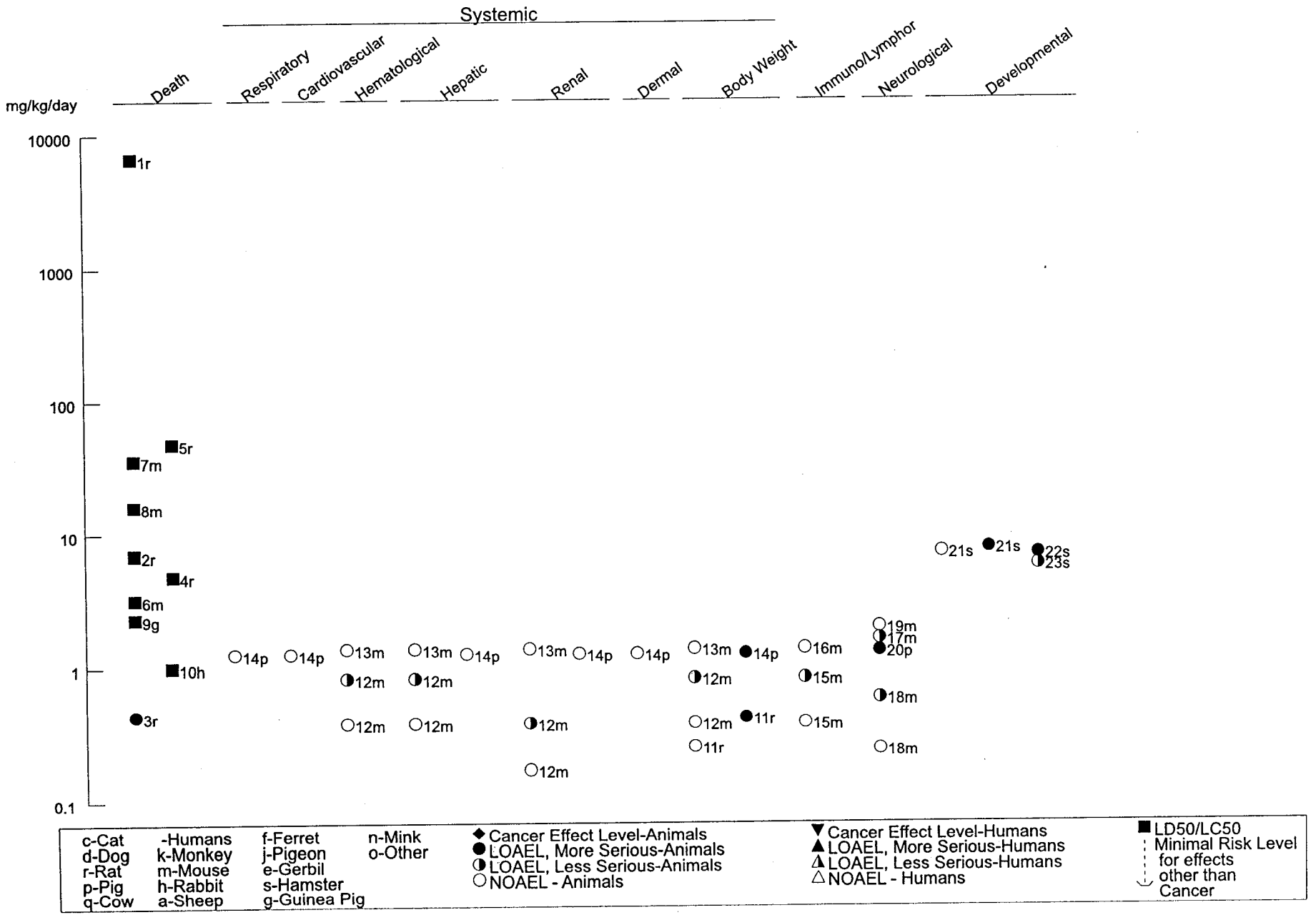


Figure 3-2. Levels of Significant Exposure to Selenium - Oral (*continued*)

Intermediate (15-364 days)

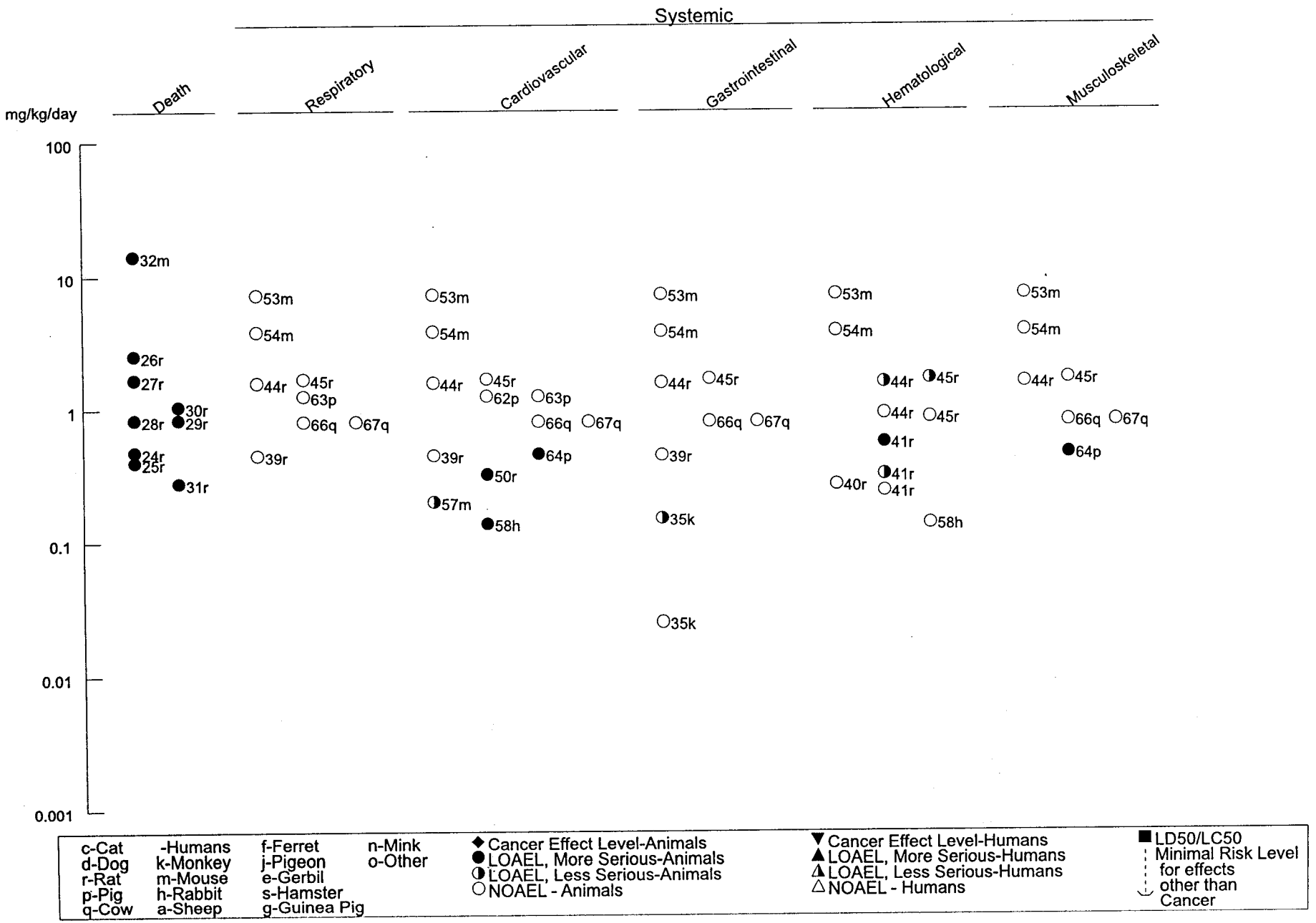


Figure 3-2. Levels of Significant Exposure to Selenium - Oral (*continued*)

Intermediate (15-364 days)

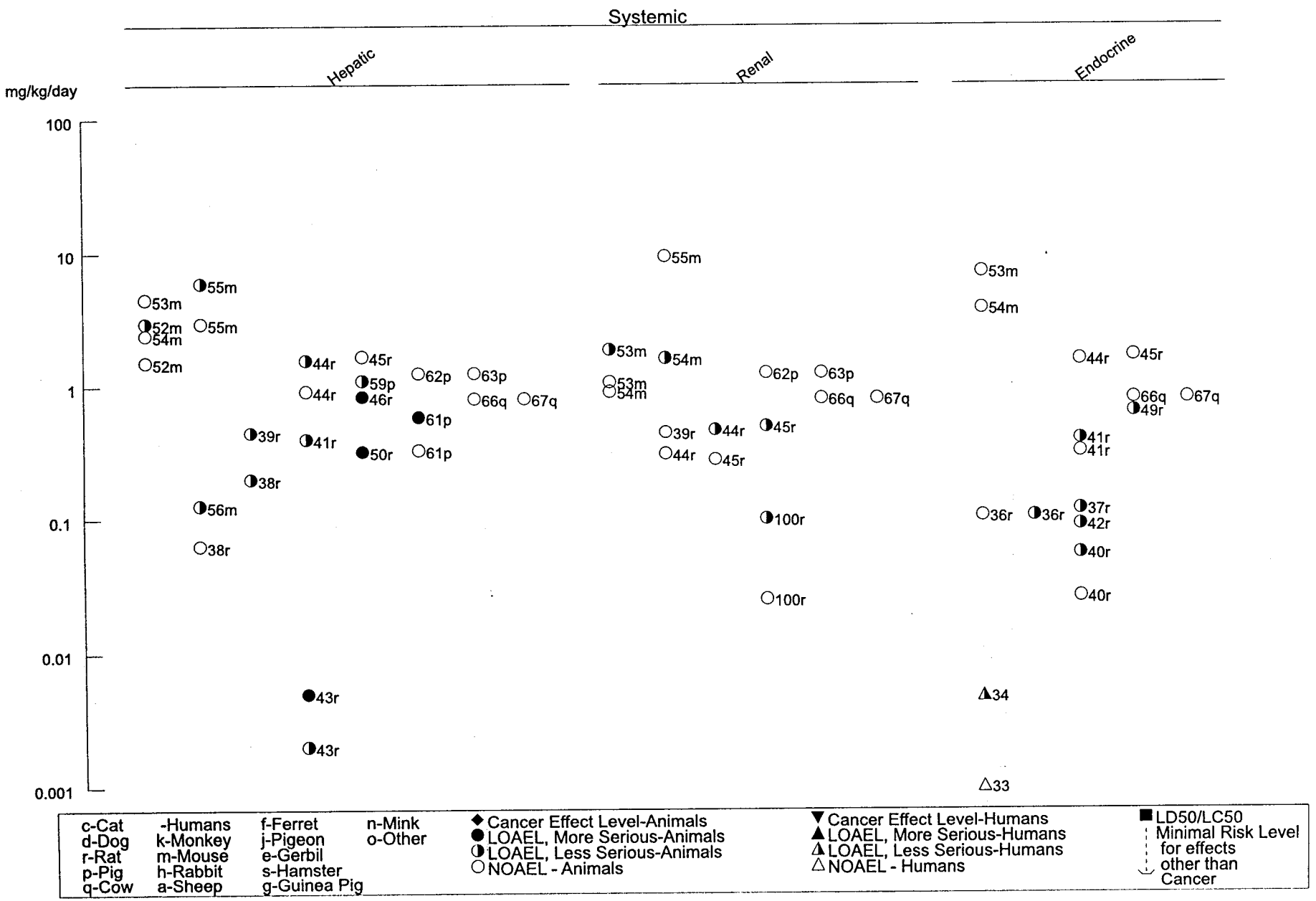


Figure 3-2. Levels of Significant Exposure to Selenium - Oral (*continued*)

Intermediate (15-364 days)

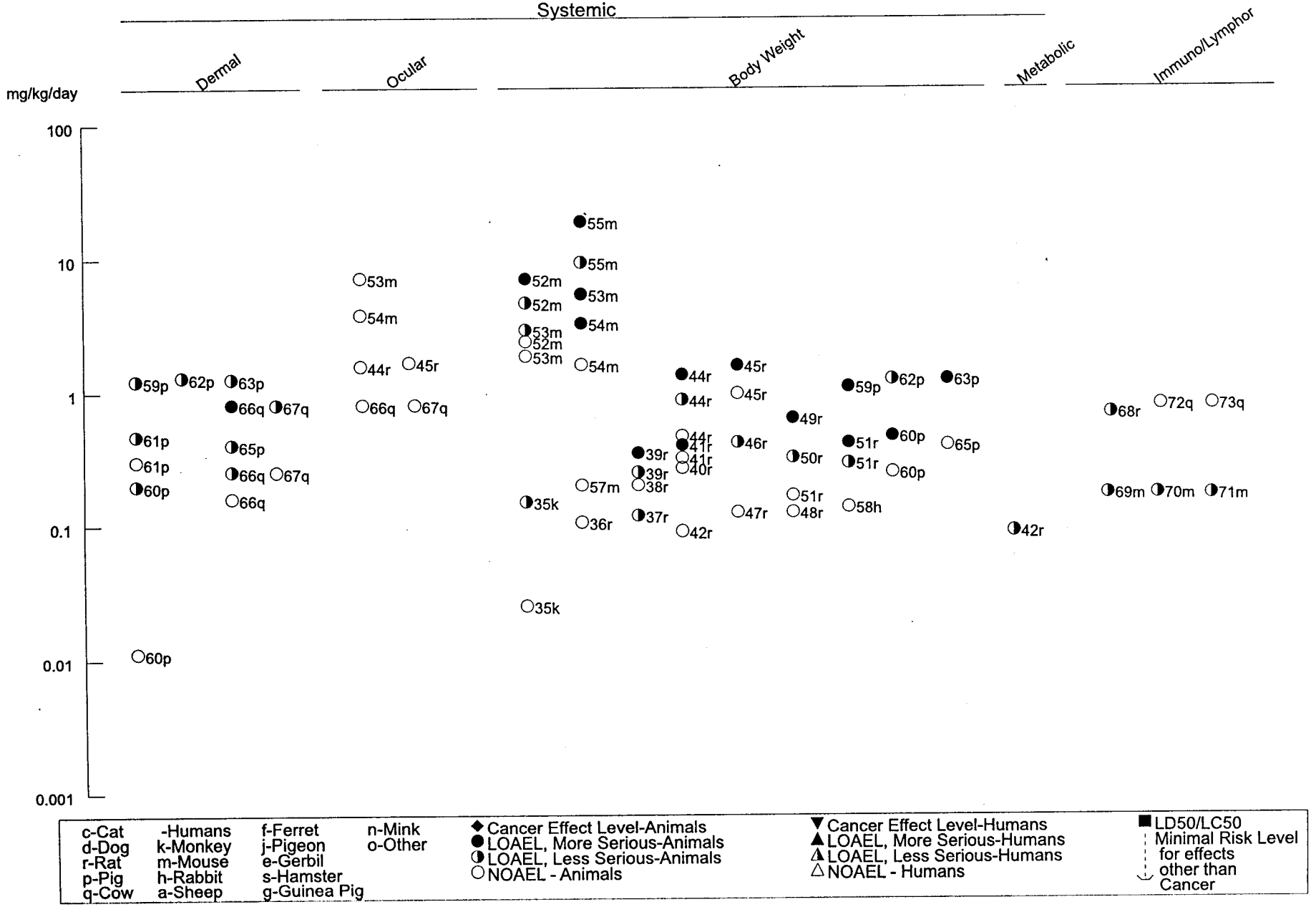


Figure 3-2. Levels of Significant Exposure to Selenium - Oral (*continued*)

Intermediate (15-364 days)

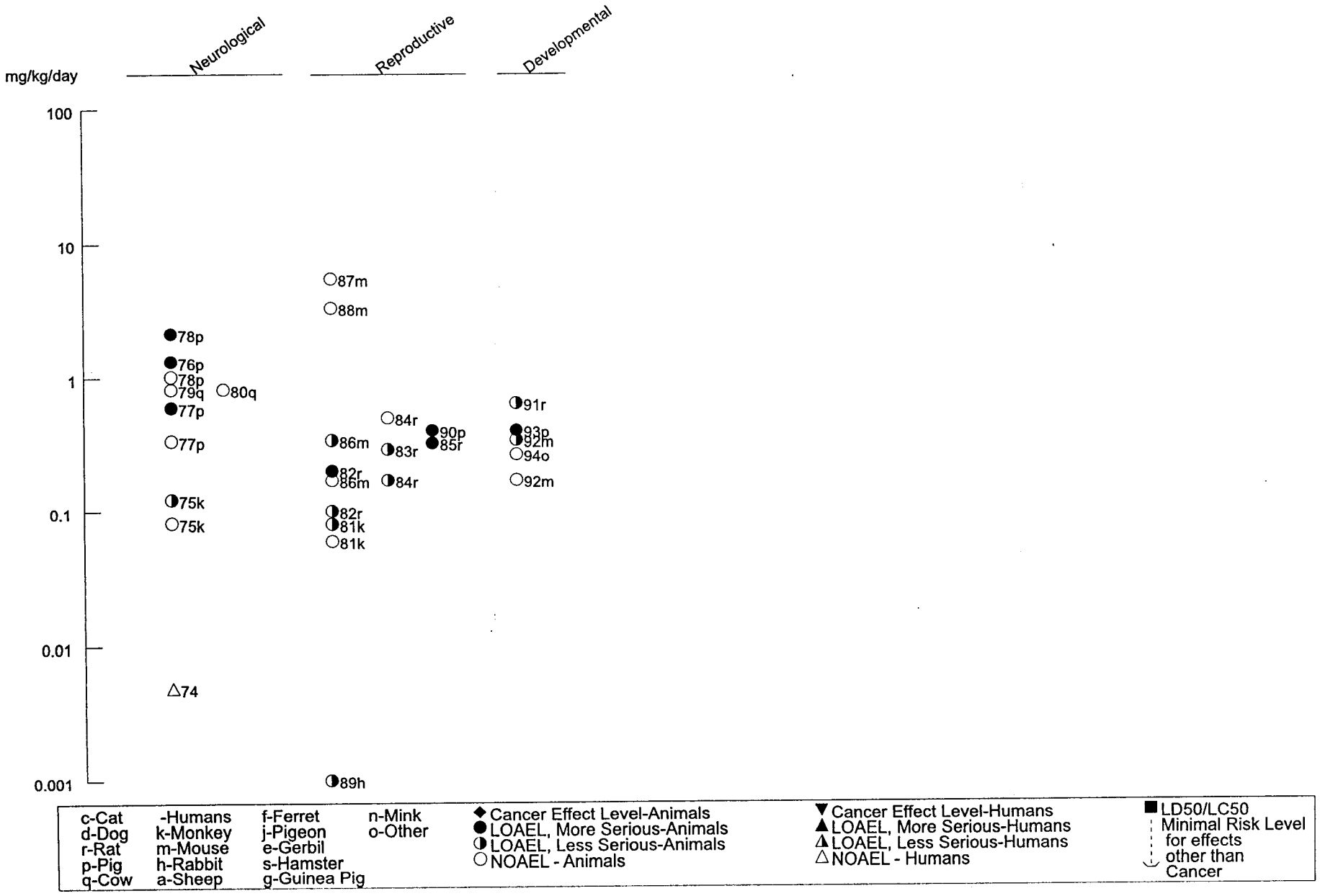


Figure 3-2. Levels of Significant Exposure to Selenium - Oral (*continued*)

Chronic (≥365 days)

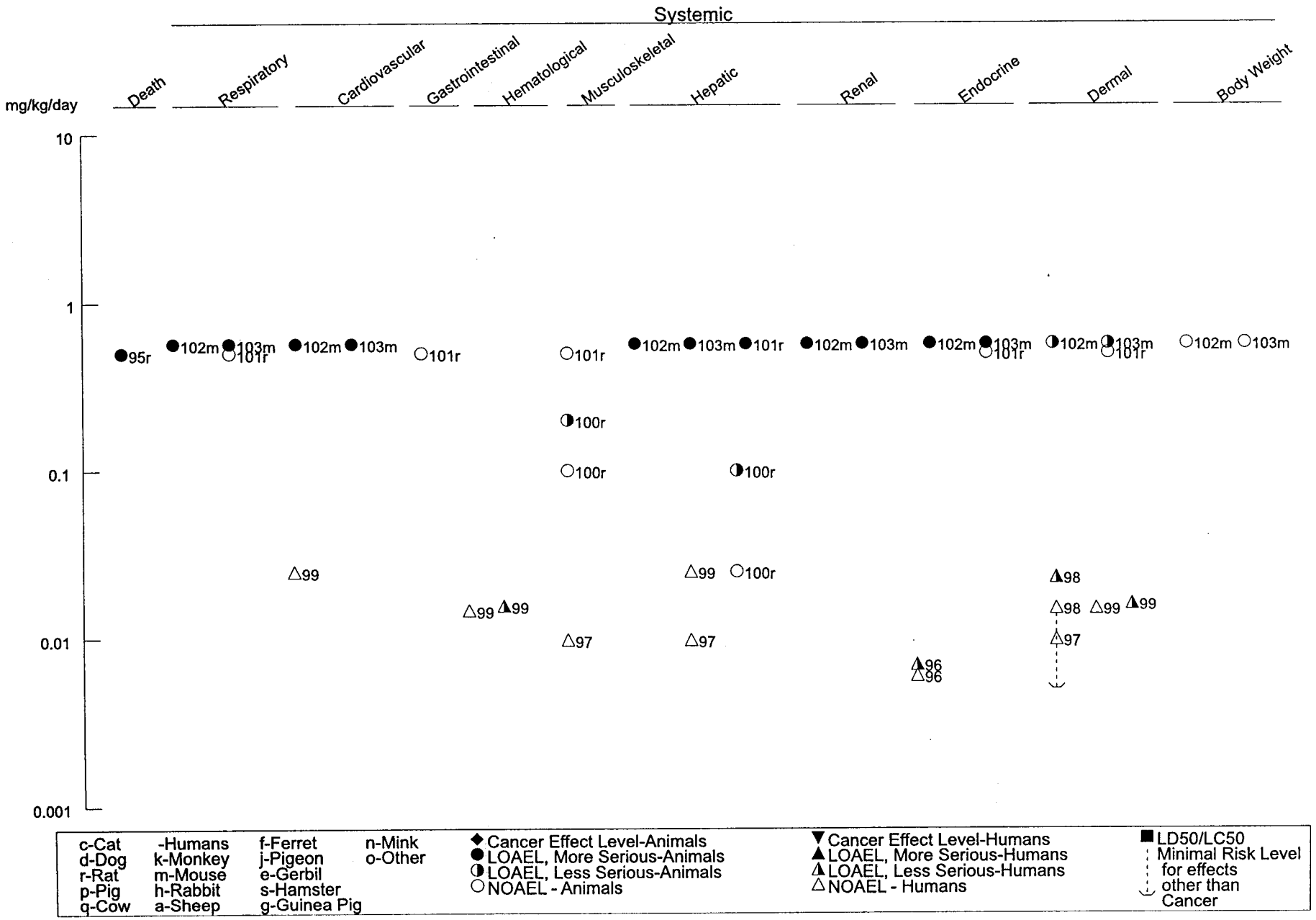


Figure 3-2. Levels of Significant Exposure to Selenium - Oral (*continued*)

Chronic (≥365 days)

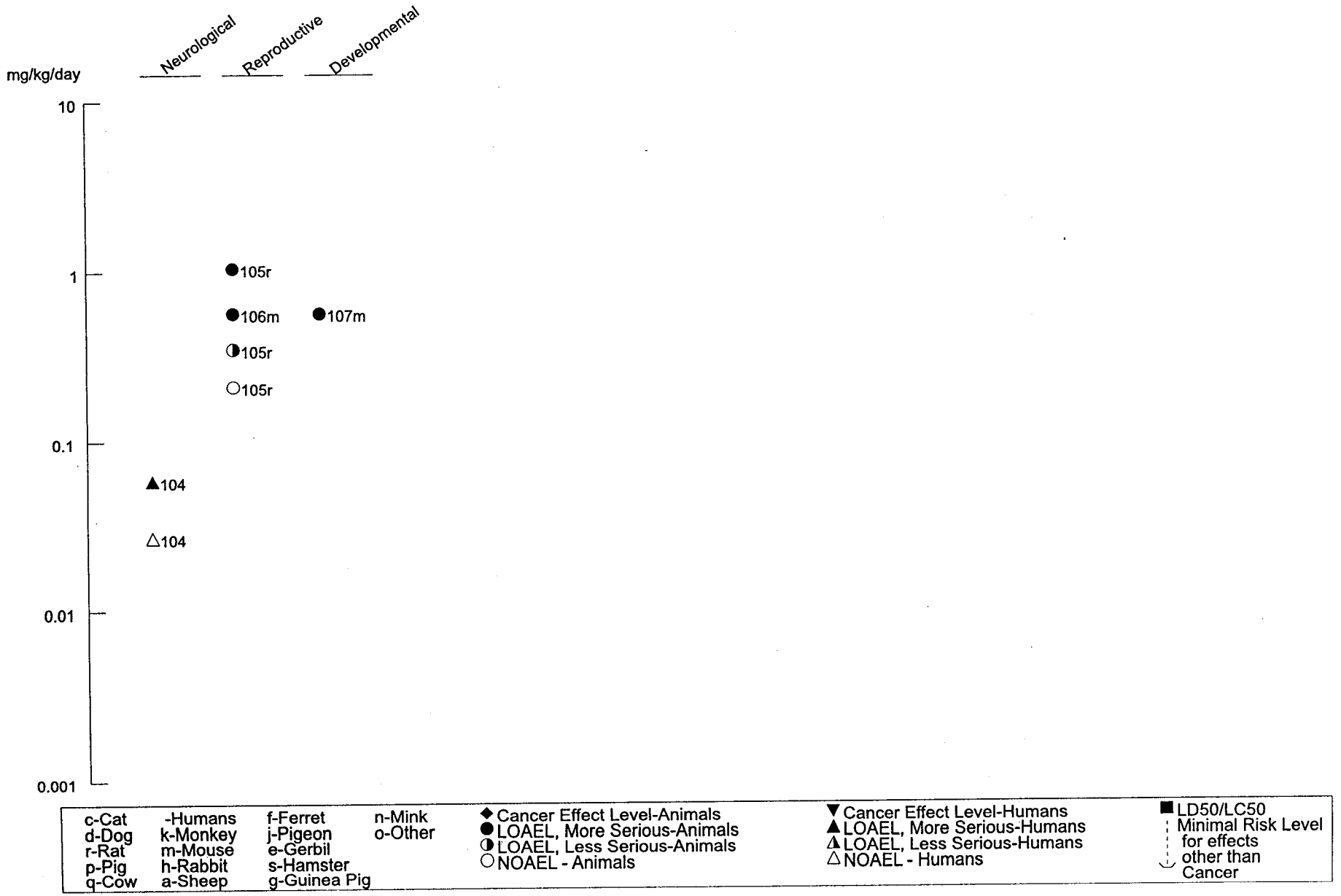


Table 3-3. Levels of Significant Exposure to Selenium Sulfides - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Sprague-Dawley)	once (G)				138 M (LD_{50})	Cummins and Kimura 1971 SeS_2 (aqueous)
2	Rat (Wistar)	once (GO)				75 M (3/6 died)	Moore et al. 1996b SeS
3	Rat (Wistar)	once (GO)				50 (3/15 died)	Moore et al. 1996b SeS
4	Mouse (NMRI)	once (G)				3700 (LD_{50})	Henschler and Kirschner 1969 SeS
	Systemic						
5	Rat (Wistar)	once (GO)	Hepatic			75 M (widespread hepatic necrosis)	Moore et al. 1996b SeS

Table 3-3. Levels of Significant Exposure to Selenium Sulfides - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	INTERMEDIATE EXPOSURE						
	Death						
6	Rat (Fischer- 344)	17 d 1x/d (G)				112 M (LD_{50})	NTP 1980c SeS, SeS_2
						56[b] F (LD_{50})	
7	Mouse (B6C3F1)	17 d 1x/d (G)				805 M (LD_{50})	NTP 1980c SeS, SeS_2
						316[b] F (LD_{50})	
	Systemic						
8	Rat (Fischer- 344)	13 wk 7d/wk 1x/d (G)	Resp	31.6			NTP 1980c SeS, SeS_2
			Cardio	31.6			
			Gastro	31.6			
			Musc/skel	31.6			
			Hepatic	17.6	31.6 (focal necrosis)		
			Renal	31.6			
			Endocr	31.6			
			Dermal	31.6			
			Bd Wt	31.6			

Table 3-3. Levels of Significant Exposure to Selenium Sulfides - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)	
9	Mouse (B6C3F1)	13 wk 7d/wk 1x/d (G)	Resp	464				NTP 1980c SeS, SeS_2
			Cardio	464				
			Gastro	464				
			Musc/skel	464				
			Hepatic	464				
			Renal	216	464	(interstitial nephritis)		
			Endocr	464				
			Dermal	464				
			Bd Wt	216 F	464 F	(body weight 17% lower than controls)		

Table 3-3. Levels of Significant Exposure to Selenium Sulfides - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)	
CHRONIC EXPOSURE								
Cancer								
10	Rat (Fischer- 344)	103 wk 7d/wk 1x/d (G)					15 (hepatocellular carcinomas 14/49 males, 21/50 females)	NTP 1980c SeS, SeS_2
11	Mouse (B6C3F1)	103 wk 7d/wk 1x/d (G)					100 F (hepatocellular carcinomas/adenomas 25/49, alveolar/bronchiolar carcinoma/adenomas 12/49)	NTP 1980c SeS, SeS_2

[a]The number corresponds to entries in Figure 3-3.
[b]Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

ad lib = ab libitum; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr - endocrine; F = female; gastro = gastrointestinal; (G) = gavage; gd = gestation day; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; (W) = water; wk = week(s); x = time(s); yr = year(s)

Figure 3-3. Levels of Significant Exposure to Selenium Sulfides - oral

Acute (≤14 days)

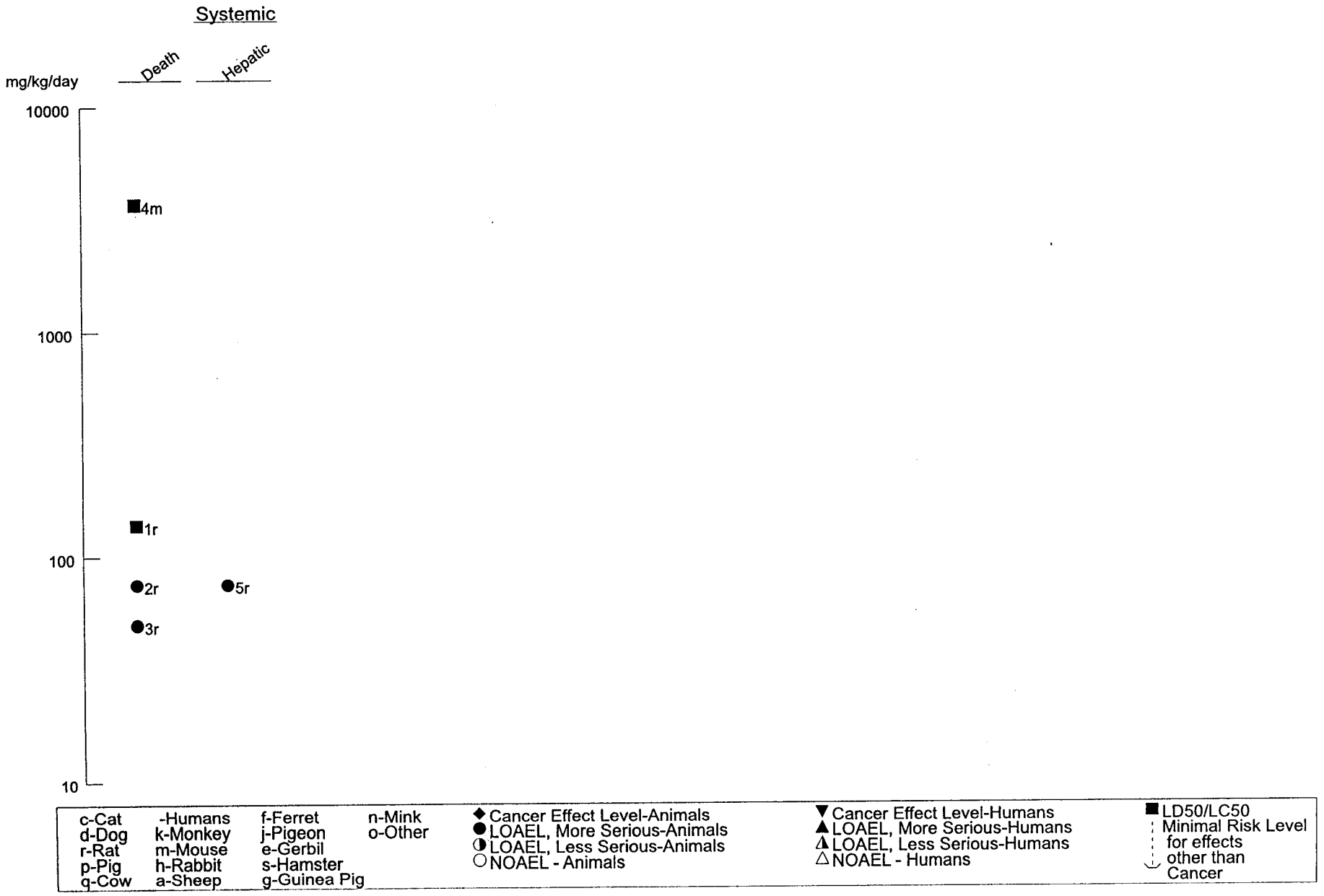


Figure 3-3. Levels of Significant Exposure to Selenium Sulfides - oral (*continued*)

Intermediate (15-364 days)

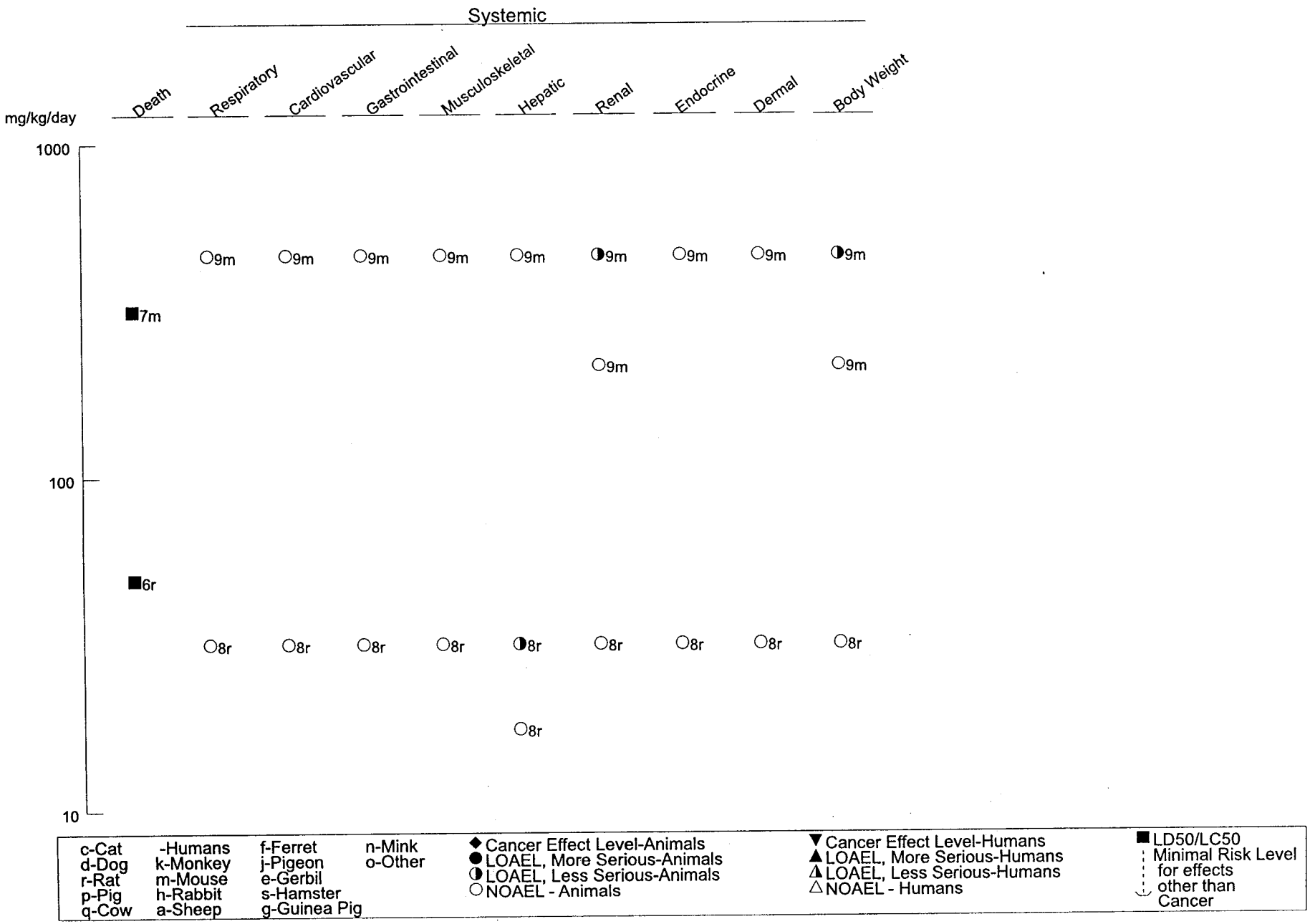
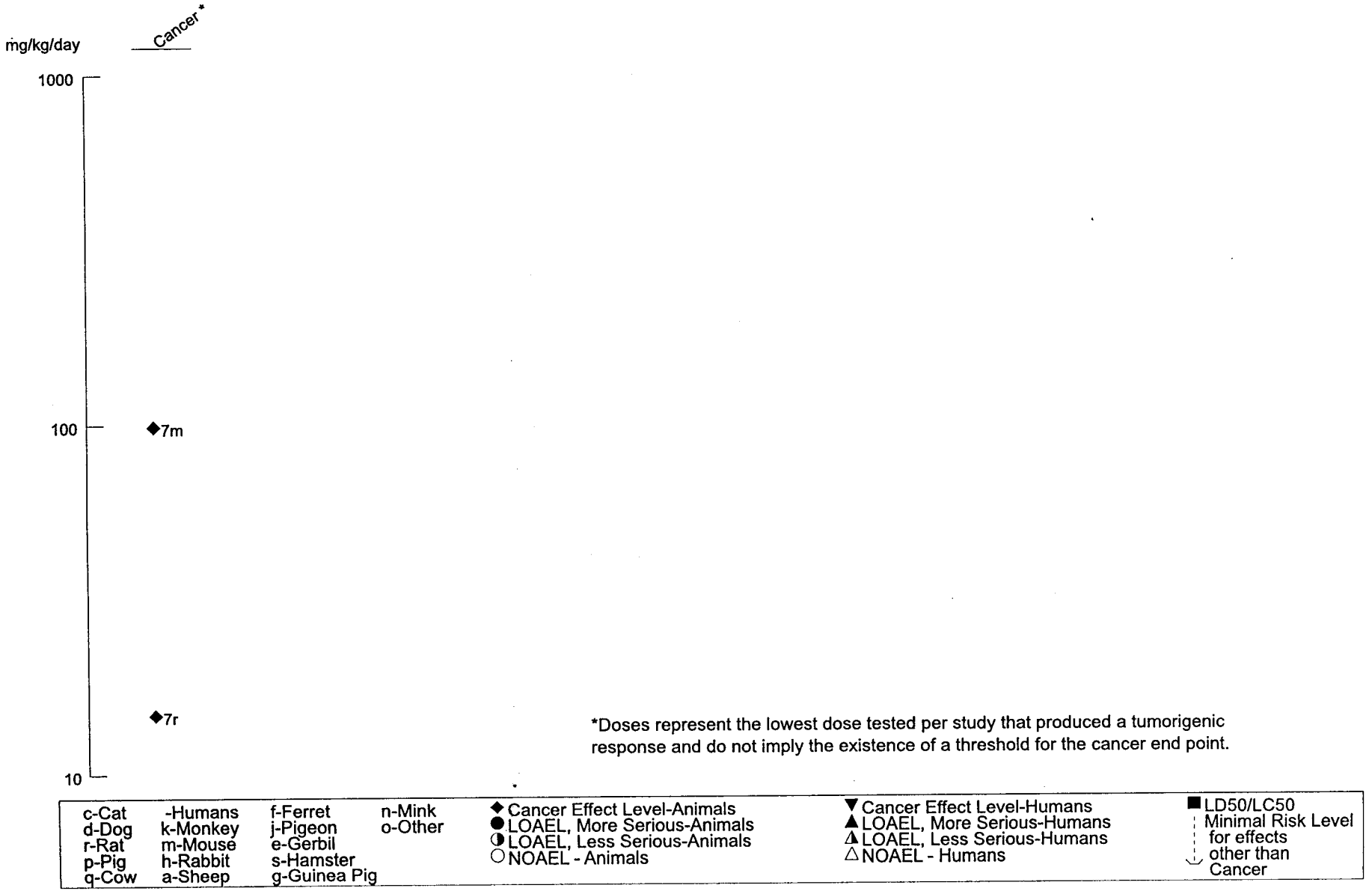


Figure 3-3. Levels of Significant Exposure to Selenium Sulfides - oral (*continued*)

Chronic (≥365 days)



Most of the available toxicity information for oral exposures to selenium compounds comes from domestic or experimental animal exposures to selenite, selenate, selenium sulfides (mixed), and organic selenium compounds (selenocystine, selenomethionine). Some of the earliest recognized effects of selenium were observed in livestock that grazed on plants in areas of South Dakota, where soil selenium concentrations are naturally high. Selenium-associated effects observed in livestock include blind staggers and alkali disease. Blind staggers is an acute disease in which there is usually a slight impairment of vision, which can result in the animal straying from the herd. As the disease progresses, the blindness becomes more pronounced, and the animal may wander in circles. In the last stage there are various degrees of paralysis, and evidence of abdominal pain; death results from respiratory failure. Alkali disease is a chronic disease in which the animals become emaciated, stiff, and lame; lose long hair from the mane and the tail; and the hooves become deformed. Alkali disease is also associated with atrophy of the heart and liver, while congestion and focal necrosis of the liver are more prominent in blind staggers.

Some epidemiological studies report data from populations exposed to selenium in the food chain in areas with high selenium levels in soil. It is likely that selenite, selenate, and the selenium found in food and in dietary supplements comprise the majority of selenium compounds to which oral, off-site selenium exposures will occur at or near hazardous waste sites. Aside from the variation in effective dose, the health effects from exposure to selenate, selenite, and dietary selenium are not expected to differ greatly. However, oral exposures to many other compounds of selenium could occur (primarily through soil or edible plant ingestion) if those compounds were deposited at the site, or if local environmental conditions greatly favor transformation to those forms. Heavy metal selenides, aluminum selenide, tungsten diselenides, and cadmium selenide are used in industry and may end up in waste sites.

3.2.2.1 Death

Accidental selenium poisonings in humans have occurred, but few fatalities have been reported. The selenium doses associated with the reported deaths are unknown (Carter 1966; Koppel et al. 1986). One 3-year-old boy died 1.5 hours after ingestion of an unknown quantity of selenious acid contained in a gun-blueing preparation (Carter 1966). Clinical signs included excessive salivation, garlic odor on the breath, and shallow breathing. A 15-year-old female survived ingestion of a solution of sodium selenate estimated to have provided 22 mg selenium/kg body weight, probably because she was forced to vomit soon after exposure (Civil and McDonald 1978). Clinical signs included garlic odor of the breath and diarrhea.

No cases of human death in the United States have been attributed to intermediate or chronic oral exposures to selenium or selenium compounds. In the Hubei Province of China, in an area of endemic selenosis, a woman who died was suffering from hemiplegia thought to have been caused by chronic selenosis induced by eating locally grown foods that contained high levels of organic selenium compounds (Yang et al. 1983). However, an autopsy was not performed and no clinical history of previous illness was available.

In nonhuman animals, the most acutely toxic selenium compounds by ingestion appear to be sodium selenite and sodium selenate (Olson 1986). Oral LD_{50} values for sodium selenite, expressed as mg selenium/kg body weight, were reported as 4.8–7.0 in rats, 1.0 in rabbits, 3.2 in mice, and 2.3 in guinea pigs (Cummins and Kimura 1971; Pletnikova 1970). Minimum lethal doses of sodium selenite, expressed as mg selenium/kg body weight, reported for larger animals were 13–18 for pigs and 9.9–11.0 for cows (Miller and Williams 1940); however, these values were estimated on the basis of a small number of animals. Two of four 12-week-old lambs died within 16 hours of administration of 5 mg selenium/kg as sodium selenite (Smyth et al. 1990). Selenium dioxide is reported to have LD_{50} values of 16 mg selenium/kg for mice and 48 mg selenium/kg body weight for rats, but these values are also based on a small number of animals (Singh and Junnarkar 1991). An oral LD_{50} of 35.9 mg selenium/kg has been reported for L-selenocystine given to mice (Sayato et al. 1993). Elemental selenium is less toxic than most selenium compounds, because of its extremely low solubility; an LD_{50} of 6,700 mg selenium/kg body weight has been reported for oral administration of elemental selenium as a suspension (particle size 1–30 m) in 0.5% methylcellulose to rats (Cummins and Kumura 1971).

Lower doses of selenium can cause signs of toxicity if administered over extended periods of time. Eight weaned 5-week-old pigs receiving 1.3 mg selenium/kg/day as sodium selenite in gelatin capsules daily for 10 days died during one study; only one dose level was tested (Wilson et al. 1989). Two long-tailed macaques administered 0.60 mg selenium/kg/day as selenomethionine by nasogastric intubation died of either anorexia or aspirated vomitus secondary to emesis and gastritis after 10 or 15 days of treatment (Cukerski et al. 1989). Seven of 12 female rats receiving diets containing 0.418 mg selenium/kg/day as sodium selenate for 14 days died before the end of the experiment (NTP 1996). Exposure to selenium in drinking water at a level of 0.84 mg selenium/kg/day as selenite or selenate for 4–6 weeks resulted in the death of four of six or two of six male rats, respectively (Palmer and Olson 1974). Feeding male rats diets containing 0.48 mg selenium/kg/day as sodium selenite or 0.4 mg selenium/kg/day as seleniferous wheat for 6 weeks resulted in the death of one of eight rats in each group (Halverson et al. 1966). Administration of sodium selenite in drinking water at a level of 0.28 mg selenium/kg/day for 58 days

resulted in the death of 25 of 50 male rats (Schroeder and Mitchener 1971a). Mortality was observed in rats, but not in mice, receiving either 1.67 mg selenium/kg/day as sodium selenite or 2.54 mg selenium/kg/day as sodium selenate in drinking water for 13 weeks (NTP 1994). Gavage treatment of male mice with selenocystine 6 days per week for 30 days at a dose of 14.2 mg selenium/kg killed all 15 treated animals, while no deaths were noted at 9.4 mg selenium/kg (Sayato et al. 1993). The longevity of hamsters, was not affected by dietary administration of sodium selenite at a dose of 0.42 mg selenium/kg/day for 124–144 weeks (Birt et al. 1986).

Sodium selenate and sodium selenite exhibit similar toxicity in female rats, but male rats appear more susceptible to the toxicity of sodium selenite than selenate (Palmer and Olson 1974; Schroeder and Mitchener 1971a). Sodium selenate in drinking water at 0.28 selenium mg/kg/day for 1 year did not increase mortality of male or female rats compared with control rats (Schroeder and Mitchener 1971a). Ingestion of 0.28 mg selenium/kg/day of sodium selenite in drinking water for 1 year did not increase mortality in female rats, whereas 50% of the males died by day 58 of administration (Schroeder and Mitchener 1971a).

The relative acute toxicities of sodium selenite, potassium selenite, sodium selenate, and potassium selenate in aqueous solution have been examined in mice (Pletnikova 1970). No significant differences among the toxicities of the potassium and sodium salts of selenium were apparent in this study. In another study, rats tolerated a dose of 1.05 mg selenium/kg/day administered in drinking water as potassium selenate for over 8 months with no deaths, but three of five females and one of three males died by the end of 1 year (Rosenfeld and Beath 1954). Decreased survival was reported in rats fed sodium selenate or selenite at 0.5 mg selenium/kg/day in a 2-year cancer study (Harr et al. 1967; Tinsley et al. 1967). No mortality was observed in hamsters fed 0.42 mg selenium/kg/day as sodium selenite in the diet for 82–142 weeks (Birt et al. 1986).

Selenium sulfide (i.e., selenium monosulfide) and selenium disulfide are less water soluble and are of lower acute toxicity than sodium selenate or sodium selenite. There are no reported human deaths due to ingestion of selenium sulfide. The LD_{50} value for the gavage administration of 1–20% selenium disulfide in aqueous 0.5% methylcellulose to rats was 138 mg selenium disulfide/kg (Cummins and Kimura 1971). When 1% selenium disulfide shampoo was administered by gavage, the LD_{50} value was lower (78 mg selenium disulfide/kg) (Cummins and Kimura 1971). The compound administered may have been a mixture of selenium sulfide and selenium disulfide; analysis of the compound was not reported. Henschler and Kirschner (1969) reported an LD_{50} of 3,700 mg selenium sulfide/kg for mice administered

by gavage in aqueous 0.5% carboxymethylcellulose. Administration of single gavage doses of selenium monosulfide to rats produced death in 3/15 animals dosed with 50 mg/kg, 3/6 animals dosed with 75 mg/kg, 1/2 animals dosed with 100 mg/kg, and 2/2 animals dosed with 125 mg/kg (Moore et al. 1996b).

In the case of selenium sulfide, mice are more tolerant than rats, and males of both species appear to be more tolerant than females (NTP 1980c). The daily doses producing 50% mortality for a 17-day gavage administration of a mixture of selenium mono- and disulfides were 112 mg selenium sulfides/kg for male rats, 56 mg selenium sulfides/kg for female rats, and 805 mg selenium sulfides/kg for male mice (NTP 1980c). A 13-week gavage study using the same mixture of selenium mono- and disulfides reported survival as 10/10, 10/10, 10/10, 9/9, 8/9, and 6/10 in female mice and 10/10, 10/10, 10/10, 10/10, 10/10, and 9/10 in male mice receiving 0, 21.6, 46.4, 100, 216, and 464 mg selenium sulfides/kg/day, respectively (NTP 1980c). Although the researchers intended to administer selenium monosulfide to the animals, elemental analysis, melting point, and x-ray diffraction revealed that the compound administered included some selenium disulfide. No other chemical or physical analyses of the selenium compound administered were reported.

The LD_{50} and lethal LOAEL values from each reliable study following oral exposure to elemental selenium dust, selenium dioxide dissolved in water (selenious acid), sodium selenate, sodium selenite, potassium selenate, and dietary selenium for each species and exposure duration are recorded in Table 3-2 and plotted in Figure 3-2. The LOAEL values for death in rats and mice following acute and intermediate oral exposures to selenium sulfide or selenium disulfide are recorded in Table 3-3 and plotted in Figure 3-3.

3.2.2.2 Systemic Effects

The highest NOAEL value and all LOAEL values for each reliable study for systemic effects in each species and duration category are recorded in Tables 3-2 and 3-3 and plotted in Figures 3-2 and 3-3.

Respiratory Effects. Pulmonary edema and lesions of the lung have been noted in case reports of humans (Carter 1966; Koppel et al. 1986) and other animals (Glenn et al. 1964a; Rosenfeld and Beath 1947) after ingestion of lethal doses of selenium compounds. Rabbits orally administered sodium selenite (subroute not specified) at levels approximating the LD_{50} (1–5 mg selenium/kg body weight) developed pulmonary congestion, hemorrhages, and edema; dyspnea; general muscular weakness; and asphyxial

convulsions (Smith and Westfall 1937). Pulmonary edema and hemorrhages were observed in four sheep treated orally (subroute not specified) with a single dose of sodium selenite of 5 mg selenium/kg (Smyth et al. 1990). The lungs may be a target of acute exposure to excess selenium because the metabolite, dimethyl selenide, is exhaled.

The effects of intermediate or chronic exposures to selenium compounds are less clear. Although Harr et al. (1967) stated that absolute lung weights decreased with increasing doses of selenite or selenate chronically administered to rats in the diet in a 2-year cancer study, but they did not report lung weights at specific dose levels. Selenium administration also might have contributed to pneumonic lesions, but again, the authors did not statistically analyze their results or relate the severity of the effect to the doses of selenium administered. Respiratory effects were not observed in rats treated with selenite in the diet for 8 weeks at a dose of 0.45 mg selenium/kg/day (Chen et al. 1993). Effects on the lungs were not observed in pigs fed 1.25 mg selenium/kg as organic selenium found in the plant *Astragalus bisulcatus* for up to 5 days, or D,L-selenomethionine or selenate in the diet for up to 6 weeks (Panter et al. 1996). Treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days did not produce any signs of respiratory distress or changes in lung weight or histology (O'Toole and Raisbeck 1995). Ingestion of selenium in drinking water for 13 weeks at doses up to 1.67 and 7.17 mg selenium/kg as selenate in rats and mice, respectively, and 1.57 and 3.83 mg selenium/kg as selenite in rats and mice, respectively, did not cause any respiratory effects (NTP 1994). Nelson et al. (1943) reported that no effects on the lungs were apparent in rats administered 0.50 mg selenium/kg/day as seleniferous corn for 2 years.

An increased incidence of amyloidosis of the major organs, including the lungs, was observed in mice following lifetime exposure to sodium selenate or sodium selenite in drinking water at a level of 0.57 mg selenium/kg/day (Schroeder and Mitchener 1972). This effect was noted in 30% of control mice and 58% ($p<0.001$) of selenium-treated mice. Data for individual organs were not provided.

Administration of lethal doses of selenium sulfide particles in carboxymethylcellulose by gavage has been reported to cause irregular breathing in mice (Henschler and Kerschner 1969), but not in rats (Cummins and Kimura 1971). No respiratory effects were seen in mice administered 464 mg selenium sulfides/kg/day or in rats administered 31.6 mg selenium sulfides/kg/day by gavage once daily for 13 weeks (NTP 1980c).

Cardiovascular Effects. Tachycardia has occasionally been reported as a result of a lethal, acute oral exposure to selenium compounds in humans (Carter 1966); however, the dose was not reported in this lethal exposure to a gun-blueing solution containing selenious acid. Although myocardial disorders (cardiogenic shock, congestive heart failure, arrhythmia, multifocal necrosis of the myocardium) have been associated with selenium deficiencies (Yang et al. 1988), none has been reported to be associated with chronic dietary selenosis in humans observed at doses of 0.016 mg/kg/day and greater (Yang et al. 1989a).

In contrast, postmortem studies of sheep that died from acute oral exposure to sodium selenite or sodium selenate, have revealed petechial hemorrhages of the endocardium (Glenn et al. 1964a; Smyth et al. 1990). The sheep were treated with a time-weighted average dose of 0.65 or 0.9 mg selenium/kg/day as selenate over a 171-day period (Glenn et al. 1964a, 1964b), or a single dose of selenite at 5 mg selenium/kg (Smyth et al. 1990). Vacuolation and pyknosis of nuclei were observed in the hearts of pigs fed an unspecified form of selenium at a dose of 0.46 mg selenium/kg/day for 34 days (Stow et al. 1992). In a two year cancer study, Harr et al. (1967) reported the occurrence of myocardial hyperemia, hemorrhage, and degeneration, as well as pericardial edema, in young rats administered sodium selenite or sodium selenate in the feed at doses of 0.5 mg selenium/kg/day, although the authors did not specify the duration of exposure required to produce the effects.

Exposure of pigs to feed containing 54 mg/kg selenium for 1–7 days resulted in severe toxicity and death of several of the animals (Penrith and Robinson 1996). Histological examination of heart tissue from pigs that died revealed myocardial lesions consisting of widespread hypertrophy, atrophy, and disorganization of fibers, occasional fibrosis, and marked medial hypertrophy of the arterioles.

Wistar rats administered 0.324 mg selenium/kg/day as sodium selenite in food for 12–14 weeks showed severe diffuse degenerative changes, including edema in the sub-endocardial connective tissue and the interfibers of prevascular regions, and myofibril swelling with profuse intercellular edema (Turan et al. 1999a). Myocyte borders were irregular, and there was a loss of striations and a degeneration of the sarcolemma and myofibril structure and order. Examination of the mechanical function of the heart *in vitro* using either Langendorff perfusion or papillary muscle recordings showed increased coronary perfusion pressure, increased resting force, and increased heart rate with irregular beating. No difference in contractile force was observed. Chronic heart failure did not occur in any of the animals in the study.

Cardiac damage was also observed in mice exposed to 0.2 mg selenium/kg/day as sodium selenite in food for 12 weeks (Skowerski et al. 1997b). Ultrastructural examination revealed cardiomyocytes that had numerous damaged mitochondria, a large number of lipid droplets, and numerous lysosomes.

Hearts of New Zealand White rabbits administered 0.137 mg selenium/kg/day as sodium selenite in food for 3 months showed distinct, degenerative changes indicating disintegration of the internal structure of the myocytes (Turan et al. 1999b). Muscle fibers were fragmented and separated. Disruption and loss of myofibrils was observed, sarcomeres were irregular, and the I, Z, and H bands were disorganized and discontinuous. Mitochondria were fewer and more variable in size and shape, with disoriented cristae and a loss of matrix substance. Hearts of control animals (0.007 mg selenium/kg/day) had normal histology.

Treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days did not produce any changes in heart weight or histology (O'Toole and Raisbeck 1995). Histopathological changes in the heart were not observed in pigs fed selenium at 1.25 mg selenium/kg as organic selenium found in the plant *A. bisulcatus* for up to 5 days, or D,L-selenomethionine or selenate for up to 6 weeks (Panter et al. 1996). Histopathological changes were not observed in the hearts of rats treated with selenite in the diet for 8 weeks at a dose of 0.45 mg selenium/kg/day (Chen et al. 1993). Selenium administered to rats and mice in drinking water for 13 weeks at doses up to 1.57 and 7.17 mg selenium/kg/day as selenate, respectively, and up to 1.67 and 3.83 mg selenium/kg/day as selenite, respectively, did not cause any histopathological changes in the heart tissue (NTP 1994). No histopathological changes were noted in mice administered 464 mg selenium sulfides/kg/day or in rats administered 31.6 mg selenium sulfides/kg/day by gavage once daily for 13 weeks (NTP 1980c).

An increased incidence of amyloidosis of the major organs, including the heart, was observed in mice following lifetime exposure to sodium selenate or sodium selenite in drinking water at a level of 0.57 mg selenium/kg/day (Schroeder and Mitchener 1972). This effect was noted in 30% of control mice and 58% ($p<0.001$) of selenium-treated mice. Data for individual organs were not provided.

Gastrointestinal Effects. In humans, gastrointestinal distress, including nausea, vomiting, diarrhea, and abdominal pain, has been reported following ingestion of aqueous sodium selenate (Civil and McDonald 1978; Gasmi et al. 1997; Helzlsouer et al. 1985; Koppel et al. 1986; Sioris et al. 1980). Two studies provided an estimate of dose. In a case report by Civil and McDonald (1978), diarrhea was observed in a 15-year-old girl about 45 minutes after she swallowed sheep drench containing selenate at a dose of about 22 mg selenium/kg. This effect was observed despite the induction of vomiting shortly

after the exposure. In a second case report of a suicide attempt, a 56-year-old man reported that vomiting, diarrhea, and abdominal pain occurred 1 hour after he ingested approximately 11 mg/kg selenium as sodium selenite (Gasmi et al. 1997). Postmortem examinations following two deaths from selenium ingestion revealed dilation of the stomach and small intestine (Carter 1966) and erosive changes of the gastrointestinal tract (Koppel et al. 1986). High (unspecified) levels of dietary selenium compounds have been implicated as causing gastrointestinal disturbances in chronically exposed humans (Smith et al. 1936), but such symptoms are not specific to selenium intoxication.

Exposure of pigs to feed containing 54 mg/kg selenium for 1–7 days resulted in severe toxicity and death of several animals. Clinical signs included anorexia and vomiting, and histological examination (70–79 days after exposure) of three of the exposed animals that died found lesions ranging from small erosions (1–2 mm diameter) to extensive mucosal necrosis (up to 100 mm diameter) near the cardia of the stomach (Penrith and Robinson 1996).

Gross necropsy of steers that died after ingestion of sodium selenite revealed severe gastrointestinal irritation (Baker et al. 1989; Maag et al. 1960). In addition, livestock exhibiting alkali disease, perhaps as a result of long-term consumption of range plants high in selenium, eat and drink less and suffer from ulcers in the upper intestinal tract (Shamberger 1986). A single oral dose of 5 mg selenium/kg as selenite caused edema and congestion of abdominal viscera in lambs (Smyth et al. 1990). However, treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days did not produce any changes in histology of the gastrointestinal tissues (O'Toole and Raisbeck 1995).

Gastrointestinal effects were not observed in rats treated with selenite in the diet for 8 weeks at a dose of 0.45 mg selenium/kg/day (Chen et al. 1993). Selenium treatment in drinking water for 13 weeks at doses up to 1.57 and 7.17 mg selenium/kg/day as selenate in rats and mice, respectively, and 1.67 and 3.83 mg selenium/kg/day as selenite in rats and mice, respectively, did not cause any gastrointestinal effects (NTP 1994). Gastrointestinal effects were not observed in rats fed organic selenium (seleniferous corn or wheat) at 0.5 mg selenium/kg/day for 24 months (Nelson et al. 1943). Vomiting and anorexia were reported in monkeys receiving 0.15 mg/kg/day selenium as L-selenomethionine by oral intubation during gestation days 20–50 (Tarantal et al. 1991).

Selenium sulfide administration by gavage at lethal levels has been reported to cause diarrhea and anorexia in rats (Cummins and Kimura 1971). No gastrointestinal effects were seen in mice administered

464 mg selenium sulfide/kg/day or in rats administered 31.6 mg selenium sulfide/kg/day by gavage once daily for 13 weeks (NTP 1980c).

Hematological Effects. In one study of exposed humans, increased prothrombin time was reported for individuals chronically exposed to doses estimated as 0.016 mg selenium/kg/day of dietary selenium (Yang et al. 1989a). However, no increase in prothrombin time was found in another study of individuals consuming diets that supplied up to 0.0098 mg/kg/day selenium (Longnecker et al. 1991). A study that compared children from seleniferous and nonseleniferous areas of Venezuela found slightly reduced (no statistical analysis was performed) hemoglobin levels and hematocrit values for the children from the seleniferous area (Jaffe et al. 1972). However, the children from the seleniferous zone had a poorer diet, consumed less milk and meat, and had a greater incidence of intestinal parasites, which may account for the differences observed.

Red blood cell counts were significantly increased in mice which received drinking water containing 9 ppm (0.82 mg selenium/kg/day) selenium as sodium selenite for 14 days (Johnson et al. 2000). However, these mice also had a severe reduction in water consumption (43%) and this may have led to a decrease in blood volume. No significant increase in red blood cell count (or decrease in water consumption) was observed for mice receiving 3 ppm (0.38 mg selenium/kg/day) selenium as sodium selenite, or up to 9 ppm (1.36 mg selenium/kg/day) selenium as selenomethionine for 14 days (Johnson et al. 2000).

No hematological changes (hemoglobin concentration, hematocrit, erythrocyte count, and cell volume) were reported for male Sprague-Dawley rats fed diets providing up to 0.27 mg selenium/kg/day as sodium selenite for 40 days (Eder et al. 1995). Increased hematocrit was observed in rats treated with selenate (1.56 mg selenium/kg/day) or selenite (1.67 mg selenium/kg/day) in the drinking water for 13 weeks, but only at concentrations that decreased water intake (NTP 1994). No effects on hematology end points were observed in mice treated with selenate or selenite in drinking water for 13 weeks at 7.17 mg selenium/kg for selenate and 3.83 mg selenium/kg/day for selenite (NTP 1994).

No difference in blood cell counts or hematological parameters were found in rabbits administered 0.137 mg selenium/kg/day as sodium selenite in the diet for 3 months, compared with control animals receiving a normal laboratory diet (Turan et al. 1999b).

A dose-related decrease in hematocrit was observed in rats fed seleniferous wheat (Halverson et al. 1966). Compared to controls, hemoglobin was decreased 23 and 79% at 0.32 and 0.56 mg selenium/kg/day, respectively. Hemoglobin reductions were most evident in the animals that had died during the experiments. In a 2-year cancer study, Harr et al. (1967) reported that the hemoglobin concentration decreased by 0.5 g/100 mL with each twofold increase of sodium selenate in the diet, but did not specify the lowest dose at which hemoglobin concentrations were significantly reduced compared to the controls (the range of selenium doses used was 0.025–0.40 mg selenium/kg/day). Hematocrit was increased in rats given selenite and selenate in drinking water for 13 weeks at concentrations that also resulted in decreased water intake (NTP 1994). No hematological effects were noted in rats or mice treated with selenate at 0.92 and 7.17 mg selenium/kg/day, respectively, or selenite at 0.86 and 3.83 mg selenium/kg/day, respectively (NTP 1994).

No studies were located regarding hematological effects in humans or other animals after oral exposure to selenium sulfide or selenium disulfide.

Musculoskeletal Effects. No adverse musculoskeletal effects were reported following chronic oral exposure of humans to dietary levels of selenium of up to 0.0098 mg selenium/kg/day (Longnecker et al. 1991).

A single oral (subroute not specified) dose of sodium selenite (5 mg selenium/kg/day) caused edema in skeletal muscles of the diaphragm in sheep (Smyth et al. 1990). Exposure of pigs to feed containing 54 mg/kg selenium for 1–7 days resulted in severe toxicity and death of several animals (Penrith and Robinson 1996). Histological examination of skeletal muscle from animals that died found damage with interstitial oedema and diffuse swelling of fibers. Livestock suffering from chronic alkali disease, a disease once common in the southwestern United States where selenium levels are high, showed lameness due to joint erosion and hoof deformation (Shamberger 1986). However, treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days did not produce any changes in muscle or bone histology (O'Toole and Raisbeck 1995). Hyperplasia of the sarcolemma nuclei and disintegration of myofibrils were observed in the skeletal muscles of pigs fed an unspecified form of selenium for 34 days (Stow et al. 1992). In a 2-year cancer study, Harr et al. (1967) fed graded doses of selenium in the form of sodium selenate or selenite to rats and reported frank osteotoxicity at doses as low as 0.2 mg selenium/kg/day given for several months (duration specified as less than 100 days). Selenium administered in drinking water for 13 weeks at doses up to 1.57 and 7.17 mg selenium/kg/day as selenate in rats and mice, respectively, and 1.67 and 3.83 mg selenium/kg as

selenite in rats and mice, respectively, failed to cause adverse musculoskeletal effects (NTP 1994). Musculoskeletal effects were not observed in rats fed seleniferous corn or wheat at 0.5 mg selenium/kg/day for 24 months (Nelson et al. 1943). No musculoskeletal effects were seen in mice administered 464 mg selenium sulfide/kg/day or in rats administered 31.6 mg selenium sulfide/kg/day by gavage once daily for 13 weeks (NTP 1980c).

Hepatic Effects. Limited data suggest that hepatotoxicity can occur in humans following acute oral exposure to sodium selenate, but no definitive studies were located regarding hepatic effects in humans after intermediate or chronic oral exposure to selenium compounds. Tests following an acute poisoning of a 15-year-old girl with sodium selenate revealed abnormally elevated serum bilirubin and alkaline phosphatase (Civil and McDonald 1978). Hepatic effects, such as changes in serum liver enzymes or liver morphology (identified by "supersonic B" examination), have not been observed in humans at chronic dietary intakes of 0.0098 mg selenium/kg/day (Longnecker et al. 1991) or 0.025 mg selenium/kg/day (Yang et al. 1989a).

Congestion and/or edema and hemorrhage in the liver have been reported in sheep following the acute oral (subroute not specified) administration of lethal levels of sodium selenate (Hopper et al. 1985) or sodium selenite (Smyth et al. 1990) and in mules and pigs following administration of lethal levels of sodium selenite (Miller and Williams 1940). A significant decrease in relative liver weight was reported for mice exposed to 9 ppm (0.82 mg selenium/kg/day) selenium as sodium selenite in drinking water for 14 days, but not to 3 ppm (0.38 mg selenium/kg/day) (Johnson et al. 2000). No effect on liver weight was observed for mice receiving up to 9 ppm (1.36 mg selenium/kg/day) selenium as selenomethionine in drinking water for 14 days (Johnson et al. 2000).

Administration of single gavage doses of selenium monosulfide to rats produced death and widespread hepatic necrosis in 3/6 animals dosed with 75 mg/kg, 1/2 animals dosed with 100 mg/kg, and 2/2 animals dosed with 125 mg/kg (Moore et al. 1996b).

Hepatic effects have also been reported following intermediate-duration exposure in pigs, but not in cattle. Pigs exposed for 7 weeks to either dietary organic selenium in dried plants (either *A. pruelongus* or *A. bisulcatus*) or sodium selenate (at 1.1 or 1.3 mg selenium/kg/day) exhibited diffuse swelling and vacuolar degeneration of hepatocytes (Baker et al. 1989). The doses used in this study reduced mean survival to only 44 days. Pigs exposed to sodium selenite in feed for 35 days at doses less than half as high as those tested by Baker et al. (1989) (0.47 versus 1.1 or 1.3 mg selenium/kg/day) exhibited no liver

damage (Mahan and Magee 1991). A study of pigs treated with 0.08, 0.33, 0.59, or 1.07 mg selenium/kg/day as sodium selenite in the feed for 8 weeks found hepatic nodules/granules in two pigs treated with 0.59 or 1.07 mg selenium/kg/day (Mihailovic et al. (1992). The lesions were diagnosed as postdystrophic atrophic cirrhosis. However, only these two severely affected pigs (one from each of the highest dose groups of 40 animals each) were selected for histopathological examination. Hepatic effects were not observed in pigs fed selenium at 1.25 mg selenium/kg as organic selenium of the type(s) found in the plant *A. bisulcatus* for up to 5 days, or D,L-selenomethionine or selenate for up to 6 weeks (Panter et al. 1996). Treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days did not produce any changes in liver weight or histology (O'Toole and Raisbeck 1995).

Alterations or cirrhosis of the liver in experimental animals following intermediate or chronic oral exposure to selenium compounds have been reported by Bioulac-Sage et al. (1992), Fitzhugh et al. (1944), Halverson et al. (1970), Harr et al. (1967), Kolodziejczyk et al. (2000), Nelson et al. (1943), and Schroeder and Mitchener (1972). Halverson et al. (1966) reported reduced liver-to-body-weight ratios and increased bilirubin in rats administered 0.44 mg selenium/kg/day for 6 weeks as naturally occurring selenium in wheat. At this level, five of eight rats died. At a dose of 0.84 mg selenium/kg/day administered as sodium selenate in drinking water for 4–6 weeks, rats developed cirrhosis of the liver (Palmer and Olson 1974). At this level, two of six rats died.

Hepatic damage was observed in mice exposed to 0.2 mg selenium/kg/day as sodium selenite in food for 12 weeks (Skowerski et al. 1997a), and ultrastructural examination showed that the cytoplasm of the hepatocytes contained extremely large and irregularly-shaped vacuoles. Wistar rats administered 0.324 mg selenium/kg/day as sodium selenite in food for 12–14 weeks showed degenerative changes to the liver (not fully described in text) (Turan et al. 1999a). Livers of rats fed 0.002 or 0.005 mg selenium/kg/day as sodium selenite for 3 months showed damage that increased with dose (Kolodziejczyk et al. 2000). Rats from the 0.002 mg selenium/kg/day group had a distinct swelling of Küpffer cells in dilated sinusoidal vessels, mainly in the proximity of portal fields, and occasional necrotic areas comprising groups of hepatocytes, while livers from rats receiving 0.005 mg selenium/kg/day showed activation and swelling of the Küpffer cells in widened sinusoidal vessels, relatively abundant infiltrations of mononuclear cells into portal canals, and sporadic areas of necrosis within individual lobules.

Young rats treated with sodium selenite in the feed for 2 months had nodular hyperplasia at a dose of 0.2 mg selenium/kg/day. However, clinical tests of liver function (bilirubin, alanine aminotransferase,

aspartate aminotransferase, alkaline phosphatase, and gamma-glutamyltransferase activities) showed no significant changes (Bioulac-Sage et al. 1992). Diffuse panlobular vacuolar changes were reported in rats fed sodium selenite in the diet for 8 weeks at 0.45 mg/kg/day (Chen et al. 1994).

In a 2-year cancer study, acute toxic hepatitis was common among rats fed sodium selenite or sodium selenate at 0.25 mg selenium/kg/day or higher (Harr et al. 1967; Tinsley et al. 1967). Liver surfaces were mottled, and parenchymatous degeneration was present. Hepatic lesions occurred at a dose as low as 0.10 mg selenium/kg/day. Absolute liver weights decreased with increasing levels of sodium selenate or sodium selenite in the diet. The average liver weight of animals administered selenate (14.5 g) was twice the average liver weight of animals administered selenite (7.2 g); however, the average liver weight of control animals was not reported, and possible dose-related hepatic effects were not discussed by these authors.

Increased serum bile acids, suggesting cholestasis, were observed in rats treated with 1.57 mg selenium/kg/day as sodium selenate in drinking water for 13 weeks, but no effects were noted at 0.92 mg/kg/day (NTP 1994). In a 13-week drinking water study, hepatic effects were not observed in mice treated with sodium selenate at 7.17 mg selenium/kg/day, in mice treated with sodium selenite at doses up to 3.83 mg selenium/kg/day, or in rats treated with sodium selenite at doses up to 1.67 mg selenium/kg/day (NTP 1994). Increased serum aspartate aminotransferase and alanine aminotransferase activities were observed in mice treated by gavage with selenocystine at doses of 9.4 mg selenium/kg/day for 30 days (Sayato et al. 1993) or 4.7 mg selenium/kg/day for 90 days (Hasegawa et al. 1994). No effects on liver enzymes were observed in mice treated with selenocystine at 4.7 mg selenium/kg/day for 30 days (Sayato et al. 1993) or at 2.5 mg selenium/kg/day for 90 days (Hasegawa et al. 1994). Chronic dietary administration of selenium as seleniferous corn or wheat at doses ranging from 0.25 to 0.50 mg/kg/day for 24 months produced cirrhosis of the liver in rats (Nelson et al. 1943).

An increased incidence of amyloidosis of the major organs, including the liver, was observed in mice following lifetime exposure to sodium selenate or sodium selenite in drinking water at a level of 0.57 mg selenium/kg/day (Schroeder and Mitchener 1972). This effect was noted in 30% of control mice and 58% ($p<0.001$) of selenium-treated mice. Data for individual organs were not provided.

Selenium sulfide administered to rats daily by gavage for 13 weeks produced focal coagulation necrosis in the liver with infiltration by inflammatory cells. These changes developed at a dose of 31.6 mg selenium sulfide/kg/day, but not at a dose of 17.8 mg selenium sulfide/kg/day (NTP 1980c). In mice, on

the other hand, oral intubation of selenium sulfide at 464 mg selenium sulfide/kg/day did not produce hepatic effects (NTP 1980c).

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to selenium or selenium compounds.

In domestic and experimental animals, renal effects have been observed following both acute and chronic oral exposures to selenium compounds. Administration of a single oral (subroute not specified) dose of sodium selenite at 5 mg selenium/kg/day produced hydropic degeneration of the kidney in sheep (Smyth et al. 1990). In a study of the toxicity of L-selenomethionine to long-tailed macaques by nasogastric intubation, two animals administered 0.24 mg selenium/kg/day aspirated vomitus secondary to emesis, developed obvious gastritis, and died of anorexia, one after 10 days and the other after 15 days of administration (Cukierski et al. 1989). Histopathologic examination of the kidneys of these animals revealed glomerulonephritis and proximal convoluted tubule nephropathy. The study authors indicated that these changes were consistent with macaque fatal fasting syndrome and may not have resulted from the direct effects of L-selenomethionine. Following long-term ingestion of plants high in selenium, livestock suffering from alkali disease exhibited nephritis (Shamberger 1986). However, treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days did not produce any changes in kidney weight or histology (O'Toole and Raisbeck 1995).

A dose-related increase in degeneration of the renal papilla (described as mild to minimal) was observed in rats treated with selenate or selenite in the drinking water at about 0.5 mg selenium/kg/day for 13 weeks (NTP 1994). No evidence of renal toxicity was observed in rats given 0.3 mg selenium/kg/day in this study. In contrast to rats, the only kidney effect noted in mice treated with sodium selenate or selenite in the drinking water was increased relative kidney weights (NTP 1994). This effect, which occurred at $1.87 mg selenium/kg/day as selenate and $1.61 mg selenium/kg/day as selenite, was only noted at doses at which drinking water intake was decreased, leading the investigators to suggest the effect may have been a result of dehydration. A similar increase in relative kidney weight associated with decreased water consumption was observed in mice consuming approximately 0.38 mg selenium/kg/day as selenite in drinking water, but no effect on kidney weight or water consumption was observed in mice consuming up to 1.36 mg selenium/kg/day as selenomethionine (Johnson et al. 2000). No renal effects were observed in pigs fed selenium at 1.25 mg selenium/kg as organic selenium found in the plant *A. bisulcatus* for up to 5 days, or D,L-selenomethionine or selenate for up to 6 weeks (Panter et al. 1996). No effects on the kidneys were observed in rats treated with selenite in the diet for 8 weeks at a dose of

0.45 mg selenium/kg/day (Chen et al. 1993). Gavage treatment of mice with selenocystine for 30 days at a dose of 9.4 mg selenium/kg/day had no adverse effect on the kidneys (Sayato et al. 1993).

Rats chronically fed selenite in the diet were reported to exhibit more frequent and more severe nephritis than those given equivalent amounts of selenate (Harr et al. 1967); however, the study authors did not quantify these observations or statistically compare data from the two groups. An increased incidence of amyloidosis of the major organs, including the kidneys, was observed in mice following lifetime exposure to sodium selenate or sodium selenite in drinking water at a level of 0.57 mg selenium/kg/day (Schroeder and Mitchener 1972). This effect was noted in 30% of control mice and 58% ($p<0.001$) of selenium-treated mice. Data for individual organs were not provided.

A mixture of selenium sulfide and selenium disulfide administered to mice daily by gavage for 13 weeks at a dose of 464 mg selenium sulfides/kg/day produced an increase in the incidence and severity of interstitial nephritis compared with the controls, whereas a daily dose of 216 mg selenium sulfides/kg did not elicit renal toxicity (NTP 1980c). In rats, selenium sulfide by oral intubation at 31.6 mg selenium sulfides/kg/day for 13 weeks did not produce renal effects (NTP 1980c).

Endocrine Effects. Thyroid hormone metabolism is the result of a balance in iodine and selenium levels. Selenium is a component of the deiodinase enzymes, including the Type I and Type II iodothyronine 5'-deiodinases, which convert the prohormone thyroxine (T4) to the active form, triiodothyronine (T3) (Köhrle 1994; St Germain and Galton 1997). Iodine deficiency can lead to hypothyroidism; but if iodine deficiency is accompanied by selenium deficiency, thyroid gland destruction may also occur (Contempré et al. 1991a; Hofbauer et al. 1997). Supplementation of individuals deficient in both iodine and selenium with selenium produces a further decrease in thyroid function, but if selenium supplementation is preceded by normalization of iodine levels, normal thyroid function is restored (Contempré et al. 1991a, 1992).

Selenium intake was reported to affect thyroid hormone levels in a dietary study of 11 men in a metabolic unit (Hawkes and Keim 1995). This study was available only as an abstract. The men (20–45 years old) were fed a diet of foods naturally high or low in selenium (double blind) for 120 days. Dietary selenium was 80 µg/day for the first 21 days, then either 13 (n=6) or 356 (n=5) µg/day for 14 weeks. Dietary energy nutrient level was equivalent to 2,800 kcal/day. Serum T3 levels decreased in the high selenium group (-11%), increased in the low selenium group (+7.5%), and were significantly different in the two groups from the third week of treatment onwards. Thyroid stimulating hormone (TSH) concentration

increased in the high selenium group (+37%) and was significantly different from the baseline levels ($p<0.06$). Despite minor adjustments of energy nutrient intake to maintain body weight, by the sixth week the high selenium group started to gain weight relative to the low selenium group. The difference between the two groups became significant after the tenth week. There was a similar increase in lean body mass in both groups. The levels of T3 and TSH remained within the normal human range for the duration of the study.

An examination of thyroid hormone levels in lactating women residing in areas of Venezuela with high levels of selenium in the soil (selenium intake ranged from 250 to 980 µg per day as estimated from selenium content of breast milk) revealed a significant decrease in serum T3 levels, as compared with women having normal selenium intakes (90–350 µg/day), but these hormone levels remained within the normal range (Brätter and Negretti De Brätter 1996). Additionally, a significant inverse correlation for selenium and serum T3 concentration was found using the Spearman Rank test. The study authors noted that the effect of selenium on T3 levels became significant at dietary intake levels of 350–450 µg/day. No significant alterations in serum T4 or TSH levels or correlations with selenium intake were found.

Twenty weeks of selenium supplementation (10, 20, 30, or 40 µg/day) of New Zealanders who normally consume a diet low in selenium (unsupplemented intake of 28–29 µg/day), but show no signs of deficiency, produced a reduction in T4 concentration in all groups (Duffield et al. 1999). However, only the differences between the 10 µg-group and controls and the combined supplemented individuals and controls were significant. T3 and TSH levels were not measured. Thyroglobulin concentration did not change significantly with supplementation.

In a study of 68 male Latvian fish consumers (Hagmar et al. 1998), a significant inverse correlation was found between serum levels of selenium and TSH. No correlation was found between serum selenium concentration and the serum concentrations of T3 or T4. No measurements were made of dietary selenium intake.

Selenium supplementation has been shown to affect type-I-deiodinase activity in male rats (Behne et al. 1992; Eder et al. 1995; Hotz et al. 1997). Exposure to 0.055 or 0.27 mg selenium/kg/day as sodium selenite in food for 40 days produced a significant decrease (approximately 50%) in serum levels of T3 and a nonsignificant reduction in type-I-deiodinase activity compared with rats receiving 0.009 or 0.026 mg selenium/kg/day (Eder et al. 1995). Exposure to 0.27 mg selenium/kg/day did not produce any

other adverse signs, such as weight loss or decreased food consumption, and serum T4 levels were similar in all groups.

Exposure of weanling male Sprague-Dawley rats to 0.09 mg selenium/kg/day as sodium selenate in food for 6 weeks produced a significant (~30%) increase in TSH, compared with controls receiving 0.009 mg selenium/kg/day (Hotz et al. 1997). Serum T3 and T4 levels and thyroid glutathione peroxidase levels were unaffected by dietary selenium. Kidney type-I-deiodinase levels were decreased (~10%) in high selenium animals compared with controls, but the differences were not significant, and liver type-I-deiodinase levels were unaffected by dietary selenium. Iodine-deficient diets produced greater thyroid glutathione peroxidase activity at each dietary level of selenium, and the greatest activity was in rats with high selenium.

No significant changes in thyroid levels of T3 or T4 were found in male Wistar rats fed diets containing high selenium (0.105 mg selenium/kg/day as sodium selenite or 0.118 mg selenium/kg/day as L-selenomethionine) for 3 months, compared with controls receiving adequate selenium (0.0015 mg selenium/kg/day as sodium selenite) (Behne et al. 1992). However, rats eating the high selenium diet showed a significant reduction in hepatic type I deiodinase activity, compared with controls, with a 29% reduction in the production rate of T3 from T4 and a 45% reduction in the production rate of 3,3'-diiodothyronine from T4.

Many studies have documented reduced body weight gain in young animals treated with selenium compounds, and abnormal weight loss in older animals (Grønback et al. 1995; Halverson et al. 1966; Harr et al. 1967; Jacobs and Forst 1981a; Johnson et al. 2000; Nelson et al. 1943; NTP 1994; Palmer and Olson 1974; Panter et al. 1996; Schroeder 1967; Tarantal et al. 1991; Tsunoda et al. 2000). There is evidence to suggest these effects may be due in part to the interactions of selenium or selenium compounds with hormones that regulate normal growth and body weight. In a 14-day study suggesting selenium may inhibit pituitary function, Thorlacius-Ussing (1990) treated nursing rats with sodium selenite in drinking water (0.64 or 0.96 mg/kg/day). The resulting decrease in the body weight gain of the pups observed at both doses may be associated with a reduction in somatomedin C levels (no other hormone levels were tested), and the weight deficiency could be reversed by administration of a growth hormone. Postweanling female Wistar rats treated with sodium selenite (0.64 mg selenium/kg/day) in drinking water for 3 or 6 weeks exhibited decreased weight gain and decreased somatomedin C serum concentrations. When the selenium supplement was removed after 3 weeks, body weight gain returned to normal, but the serum somatomedin C concentrations did not return to control levels. Growth hormone

secretion in response to growth hormone releasing factor was also reduced in the selenium-exposed group (Thorlacius-Ussing et al. 1988). A 10% reduction in body weight and a reduction in tibia lengths, compared to pair-fed controls, were found in rats provided with sodium selenite in the drinking water at 0.46 mg selenium/kg/day for 35 days (Gronbaek et al. 1995). A significant reduction in insulin-like growth factor-binding protein-3 was also noted. The investigators concluded that the reduction in growth caused by excess selenium is not due to reduced caloric intake.

Selenium administered in drinking water for 13 weeks at doses up to 1.57 and 7.17 mg selenium/kg/day as selenate in rats and mice, respectively, and 1.67 and 3.83 mg selenium/kg as selenite in rats and mice, respectively, failed to cause changes in the weights or histology of the thyroid, adrenal glands, parathyroid, or pancreas (NTP 1994).

Lambs given a single oral (subroute not specified) dose of 5 mg selenium/kg as sodium selenite exhibited cytoplasmic flocculation of the pancreas (Smyth et al. 1990). Increased pancreas weights were observed in rats fed organic selenium (seleniferous wheat) at a dose of 0.4 mg selenium/kg/day for 6 weeks (Halverson et al. 1966). Chronic exposure of rats fed sodium selenite or sodium selenate in their diet for a lifetime was associated with pancreatic damage. Although Harr et al. (1967) reported a dose-related increase in the incidence and severity of pancreatic lesions in treated rats, they did not specify the lowest dose at which pancreatic lesions were observed.

Treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days did not produce any changes in weight or histology of the pancreas, adrenal glands, thyroid, or pituitary gland (O'Toole and Raisbeck 1995).

An increased incidence of amyloidosis of the major organs, including the adrenal gland, was observed in mice following lifetime exposure to sodium selenate or sodium selenite in drinking water at a level of 0.57 mg selenium/kg/day (Schroeder and Mitchener 1972). This effect was noted in 30% of control mice and 58% ($p<0.001$) of selenium-treated mice. Data for individual organs were not provided.

Dermal Effects. Jensen et al. (1984) described both marked alopecia and the deformity and loss of fingernails in a woman who had consumed a selenium supplement containing 31 mg total selenium (in the form of sodium selenite and elemental selenium) per tablet for 77 days. The woman consumed one tablet each day in addition to vitamin supplements (vitamins C, A, D, E, B complex) and a mineral supplement "labeled as containing all 72 trace elements in undefined quantities." In epidemiological studies of

populations chronically exposed to high levels of selenium in food and water, investigators have reported discoloration of skin, pathological deformity and loss of nails, loss of hair, and excessive tooth decay and discoloration (Smith et al. 1936; Yang et al. 1983, 1989a, 1989b). The 1989 studies by Yang et al. follow up their original 1983 study of Chinese populations living in areas classified as having low-, medium-, and high-selenium exposure based on local soils and food supplies. The average and standard error of selenium intakes in the low-, medium-, and high-intake regions were 0.0012±0.00009, 0.0037±0.0004, and 0.025±0.001 mg/kg/day, respectively. The whole blood (average ± standard error) concentrations of selenium in the low-, medium-, and high-intake regions were 0.16±0.00, 0.35±0.02, and 1.51±0.05 mg/L, respectively. The estimated daily dietary selenium intake required to produce these symptoms in an area of China characterized by endemic selenosis was at least 0.016 mg selenium/kg/day (Yang et al. 1989a). This corresponds to a blood concentration of 1.054 mg/L and an estimated daily intake of 0.91 mg/day, assuming a 55-kg Chinese man or woman and using the regression analysis provided by Yang et al. (1989b). The NOAEL from the highest intake population not affected by nail disease is 0.015 mg selenium/kg/day, which corresponds to a blood concentration of 0.97 mg/L. Foods that contributed the greatest levels of selenium were smoked pork, coal-dried corn, chestnuts, pumpkin seeds, dried fruits, and garlic. It has been noted that the selenosis problem in China began when coal with high levels of selenium was burned as the main source of fuel (Whanger 1989). Food was cooked and dried over the open flame, adding selenium to the food. In addition, the people breathed large amounts of smoke, but the contribution of volatilized selenium to the total dose of selenium has not been adequately characterized (Whanger 1989). Coal was also burned on the fields as a fertilizer source. Environmental selenium concentrations in the low-, medium-, and high-intake regions were 0.37–0.48, 0.73–5.66, and 7.06–12.08 mg/kg in soil, and 370, 1,720, and 12,270 mg/L in water, respectively (Yang et al. 1989b).

No evidence of nail disease was observed in a population living on selenium-rich ranches in the western United States (Longnecker et al. 1991). Doses of selenium were calculated to be between 0.001 and 0.01 mg/kg/day, corresponding to a maximum intake of 0.724 mg/day. Whole blood selenium concentrations were 0.18–0.67 mg/kg. Although these values for the United States are consistent with studies of the Chinese population, only one or a few individuals ingested the highest doses.

The highest selenium intake for villagers in a high-selenium area of China in which endemic selenosis did not occur was estimated at 1.51 mg selenium/person/day (0.027 mg selenium/kg/day), with the average dietary selenium intake in this area of selenosis occurrence estimated to be 3.2 mg selenium/person/day (0.058 mg selenium/kg/day) (Yang et al. 1983). The lowest daily dietary selenium intake associated with

dermal effects, 0.91 mg selenium/day, was converted to equivalent daily doses from food (0.016 mg/kg/day) for presentation in Table 3-2.

Five individuals from the high selenium region of China described by Yang et al. (1989a) who had been diagnosed with overt signs of selenosis (hair loss and nail sloughing) in 1986 were reexamined in 1992 (Yang and Zhou 1994). The results of this examination showed that these individuals had recovered from selenosis (overt symptoms of nail sloughing were absent) and that the average selenium concentrations in their blood had fallen from 1,346 to 968 µg/L. The corresponding dietary intakes of selenium were 1,270 and 819 µg/day. This study has been used to establish a LOAEL of 0.023 mg selenium/kg/day and a NOAEL of 0.015 mg selenium/kg/day. Based on the occurrence of these dermal effects, a chronic oral MRL of 0.005 mg selenium/kg/day has been derived from the NOAEL, as described in the footnote in Table 3-2. This MRL is 5 times greater than the recommended dietary allowance (RDA) for selenium of 0.001 mg/kg/day.

In a 30-day study of oral administration of L-selenomethionine to long-tailed macaques, skin lesions appeared on the forearm of one of two macaques given 0.01 mg selenium/kg/day. However, the limited number of animals precludes identifying the dose as a LOAEL for dermal effects (Cukierski et al. 1989). Pigs receiving dietary administration of the same doses of selenium for 35 days exhibited hoof cracking (Mahan and Magee 1991). Symmetrical hair loss, dry scaling skin, and cracked overgrown hooves were observed in one of five pigs and three of five pigs fed sodium selenate or D,L-selenomethionine at a dose of 1.25 mg selenium/kg for up to 6 weeks, respectively (Panter et al. 1996). In an experiment limited to a duration of 5 days because of severe paralysis, similar dermal effects were not observed in pigs fed 1.25 mg selenium/kg/day as selenium contained in the plant *A. bisulcatus*. The form of selenium in *A. bisulcatus* is unknown, although Panter et al. (1996) indicate that it is nonprotein.

Exposure of pigs to feed containing 54 mg/kg selenium for 1–7 days resulted in severe toxicity and death of several animals; however none of the pigs developed coronitis or hoof separation (Penrith and Robinson 1996). Skin from four pigs with alopecia was examined about a month after exposure and was found to have epidermal thickening due to acanthosis and hyperkeratosis, vacuolar degeneration of the basal cells and acanthocytes, necrosis of individual keratinocytes, and serocellular crusts.

In the late 19th and the early 20th century, livestock grazing on plants growing on seleniferous soils in the Great Plains of the United States suffered from alkali disease attributed to the high selenium content of the plants. Alkali disease in horses, cattle, and swine is characterized by alopecia, inflammation at the

coronary band, followed by cracked or malformed hooves and rough hair coat (Draize and Beath 1935). Daily selenium intakes associated with these effects were not quantified. However, treatment of steers with selenomethionine in food at doses of 0.288 mg selenium/kg body weight/day or selenite at doses of 0.808 mg selenium/kg/day for 120 days produced hoof lesions (O'Toole and Raisbeck 1995). In intermediate-duration studies, cracked hoof walls have been observed in pigs fed selenate, selenite, or an unspecified form of selenium at doses of 0.25 mg selenium/kg/day and greater (Baker et al. 1989; Mahan and Magee 1991; Mihailovic et al. 1992; Wahlstrom and Olson 1959b). Poor quality of the hair coat has also been reported in mice administered sodium selenite or selenate in the diet at 0.57 mg selenium/kg/day (Schroeder and Mitchener 1972). Exposure of female BALB/c mice to 0.21 mg selenium/kg/day for 6 months from diets containing selenium as sodium selenite resulted in alopecia around the nose (Boylan et al. 1990).

No studies were located regarding dermal effects in humans or other animals after oral exposure to selenium sulfide or selenium disulfide.

Ocular Effects. A case control study using a hospital discharge register indicated there was no correlation between serum selenium concentrations and cataract occurrence in humans (Knekt et al. 1992). Since this is a case control study, it does not provide information on the potential dietary factors, exposure to specific selenium compounds, or duration of exposure.

Treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days did not produce any changes in the histology of the eyes (O'Toole and Raisbeck 1995). Selenium given to rats and mice in drinking water for 13 weeks at up to 1.6 and 7.2 mg selenium/kg as selenate, respectively, or 1.7 and 3.8 mg selenium/kg as selenite, respectively, did not cause any ocular effects (NTP 1994).

Body Weight Effects. Two studies reported body weight effects in humans after oral exposure to selenium. Selenium intake was found to affect body weight in a dietary study of 11 men in a metabolic unit (Hawkes and Keim 1995). The men (20–45 years old) were fed a diet of foods naturally high or low in selenium (double blind) for 120 days. Dietary selenium was 80 µg/day for the first 21 days, then either 13 (n=6) or 356 (n=5) µg/day for 14 weeks at 2,800 kcal/day. Despite minor adjustments of intake to maintain body weight, by the 6th week the high selenium group started to gain weight relative to the low selenium group, and the difference between the two groups became significant after the 10th week. A similar increase in lean body mass was observed in both groups.

A study that compared children from seleniferous and nonseleniferous areas of Venezuela found slightly reduced height and weight (no statistical analysis was performed) for the children from the seleniferous area (Jaffe et al. 1972). However, the children from the seleniferous zone had a poorer diet, consumed less milk and meat, and had a greater incidence of intestinal parasites, which may account for the differences observed.

In contrast, reduced growth rates of young animals and reduced body weight in older animals are common observations associated with oral administration of excess sodium selenate, sodium selenite, or organic selenium compounds to experimental animals (Boylan et al. 1990; Cukierski et al. 1989; Donaldson and McGowan 1989; Gronbaek et al. 1995; Halverson et al. 1966; Harr et al. 1967; Hasegawa et al. 1994; Johnson et al. 2000; Nelson et al. 1943; NTP 1994, 1996; Palmer and Olson 1974; Panter et al. 1996; Penrith and Robinson 1996; Raisbeck et al. 1996; Sayato et al. 1993; Schroeder 1967; Tarantal et al. 1991; Thorlacius-Ussing 1990, Tsunoda et al. 2000; Turan et al. 1999a). This reduction in growth is often accompanied by reduced food and water consumption, and in dietary or drinking water studies may be an effect of poor palatability of selenium compounds. However, reduced growth is also observed in gavage studies (Cukierski et al. 1989; Hasegawa et al. 1994; Sayato et al. 1993) and, as discussed under endocrine and neurological effects, the growth retardation may have an endocrine or neurotransmitter component. Selenium effects on the levels of thyroid hormones (Behne et al. 1992; Behne and Kyriakopoulos 1993; Eder et al. 1995; Hotz et al. 1997), dopamine metabolites (Tsunoda et al. 2000), somatomedin C (Thorlacius-Ussing 1990) and insulin-like growth factor–binding protein-3 (Gronbaek et al. 1995) have been observed in selenium-treated animals.

Other Systemic Effects. Urinary excretion of selenium was about twice as great in children with a high incidence of dental caries than in children with a low incidence of caries (Hadjimarkos 1969b). Possible confounding factors (e.g., fluoride status and socioeconomic status) were not considered, however. In Yang et al. (1989a), the incidence of mottled teeth in the medium- and high-selenium groups was increased, but the effect was attributed to interactions between selenium and fluoride.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding adverse immunologic or lymphoreticular effects in humans after oral exposure to selenium or selenium compounds. One study indicates lymphocyte response was enhanced, as measured by the T-lymphocyte prolific response to pokeweed mitogen in elderly people taking a selenium-enriched yeast supplement (0.0014 mg/kg/day for 6 months). However, the elderly as a group

generally tend to have both lower blood selenium concentrations and lower lymphocyte proliferation than the general population (Peretz et al. 1991).

Studies of mice, rats, and cattle suggest that exposure to high doses of sodium selenite, but not selenomethionine, may reduce immunological responses (Johnson et al. 2000; Koller et al. 1986; Raisbeck et al. 1998; Yaeger et al. 1998). BALB/c mice (five males/group) administered sodium selenite in drinking water at 0, 1, 3, and 9 ppm selenium (0.024, 0.17, 0.38, and 0.82 mg selenium/kg/day) for 14 days showed significant decreases in the relative spleen weight at 9 ppm and the relative thymus weight at 3 and 9 ppm (Johnson et al. 2000). The number of splenocytes in the spleens of the 9 ppm group was reduced by 62%. Single-cell splenocyte cultures were made from the spleens of treated animals and used to determine the effects of selenium treatment on mitogen-induced lymphocyte blastogenesis and cytokine production. Cultured splenic lymphocytes from mice exposed to 9 ppm selenite showed a significant (260%) increase in the basal rate of proliferation and a nonsignificant increase in mitogen-induced proliferation. Exposure to 9 ppm selenite also produced a significant increase in the amount of tumor necrosis factor α (TNFα) and interleukin-1β (IL-1β) produced by lipopolysaccharide (LPS)-stimulated splenic macrophages. However, the results of this experiment must be interpreted with caution as treatment with 9 ppm selenium also produced a large and statistically significant decrease in food (21%) and water (43%) consumption so that some of the effects observed (e.g., changes in organ weights) may reflect effects of dehydration rather than selenium toxicity. In contrast, similar groups of mice treated with up to 9 ppm selenium (1.36 mg selenium/kg/day) as seleno-L-methionine showed no significant changes in body weight gain, organ weights, water consumption, or food consumption compared with controls. There were no changes in the basal or mitogen-stimulated lymphocyte proliferation following treatment with seleno-L-methionine and no alteration in the production of TNFα or IL-1β from splenic macrophages.

Another study in BALB/c mice examined the effects of consumption for 47 days of drinking water containing 7 ppm selenium as selenocystine, selenomethionine, or sodium selenite on immune function (Raisbeck et al. 1998). On the 14th day of the experiment, the mice received a subcutaneous injection of ovalbumin (OVA). Examination of mitogen-stimulated blastogenesis, B-cell function, and IgG concentrations at the end of the experimental period showed a significant decrease in B-cell function for mice treated with the two organic forms of selenium and a significant reduction in the concentration of OVA-specific antibodies for animals treated with any of the three forms of selenium. Total IgG concentration and OVA-stimulated blastogenesis did not vary between groups.

Rats given sodium selenite in drinking water at 0.7 mg selenium/kg/day for 10 weeks exhibited reduced humoral antibody (IgG) production in response to an administered antigen, and reduced prostaglandin synthesis, but there was no effect on natural killer cell (NKC) cytotoxicity (Koller et al. 1986). At lower doses (0.07 or 0.28 mg selenium/kg/day), NKC cytotoxicity was significantly increased, enhancing the immune response to antigenic stimulation, although the delayed-type hypersensitivity (DTH) and prostaglandin E_2 synthesis were significantly reduced. Selenium administration did not affect the ability of resident peritoneal cells to produce interleukin IL-1. Given the enhanced NKC activity at 0.07 and 0.28 mg selenium/kg/day, but not at 0.7 mg selenium/kg/day, and given the reduced antibody and prostaglandin synthesis at 0.7 mg selenium/kg/day, the dose of 0.7 mg selenium/kg/day is identified as the lowest LOAEL. A NOAEL cannot be identified because of the conflict between enhanced NKC activity and reduced DTH and prostaglandin E_2 synthesis occurring at the same dose levels in this study.

Antibody responses to ovalbumin were significantly lower in five male antelope (*Antilocapra americana*) fed a diet containing 15 ppm selenium (a mixture of alfalfa and hay naturally high in selenium) for 164 days than in controls fed a similar diet containing only 0.3 ppm selenium, but there was no difference in total globulin concentration between groups (Raisbeck et al. 1996). No clinical signs of selenosis or treatment-associated lesions were observed in these animals.

Treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days produced symptoms of selenosis (hoof lesions), but did not produce any changes in the weight or histology of the spleen or thymus or in the histology of the lymph nodes (O'Toole and Raisbeck 1995).

Leukocyte function was significantly reduced in pregnant cows supplemented with 0.135 mg/kg/day selenium for 3 months from diets that contained 0.25 (control), 6, or 12 ppm selenium as sodium selenite. Treated animals showed a significant decrease in forced antibody production and a depression in mitogenic response compared with controls (0.005 mg selenium/kg/day) (Yaeger et al. 1998). No clinical signs of selenium toxicosis were observed in any of the cows during the experiment.

As selenium can enhance some immune system functions, selenium may have a normal physiological function in the immune system. This is supported by an 8-week study in which treatment of mice with selenium as sodium selenite (0.33 mg selenium/kg/day, dietary) resulted in enhanced ability of cytotoxic T-lymphocytes to destroy tumor cells (Kiremidjian-Schumacher et al. 1992).

No studies were located concerning immunological or lymphoreticular effects in humans or experimental animals following oral exposure to selenium sulfide or selenium disulfide.

The highest NOAEL values and all LOAEL values from each reliable study for immunological effects following oral exposure to selenium or selenium compounds for each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

Following acute oral exposure to selenium compounds in humans, aches and pains and irritability (Civil and McDonald 1978), as well as chills and tremors (Sioris et al. 1980) have been reported. The dizziness associated with selenium inhalation exposure has not been documented after selenium ingestion.

In a 1964 study, Rosenfeld and Beath reported listlessness, a general lack of mental alertness, and other symptoms of selenosis in a family exposed for approximately 3 months to well water containing 9 mg selenium/L (0.26 mg selenium/kg/day from drinking water). All of the symptoms resolved after use of the seleniferous water was discontinued. Because Rosenfeld and Beath (1964) did not estimate the family's exposure to dietary selenium, it is not possible to identify the total daily selenium dose associated with the symptoms of selenosis in this family.

In a dietary study of 11 men in a metabolic unit, selenium intake (80 µg/day for the first 21 days, then either 13 (n=6) or 356 (n=5) µg/day for 14 weeks) was reported to have no significant effect on mood, as measured using the Bi-Polar form of the profile of mood states (POMS) (Hawkes and Hornbostel 1996). However, subjects with initially low selenium levels did show significantly greater decreases in mood scores during selenium depletion.

In areas of the People's Republic of China where populations suffer from chronic selenosis, peripheral anesthesia and pain in the limbs were reported (Yang et al. 1983). In extreme cases, exaggerated tendon reflexes, convulsions, and some paralysis and hemiplegia occurred (Yang et al. 1983). These latter cases were associated with an estimated daily dietary intake of selenium of at least 3.22 mg selenium/person/day, averaging 4.99 mg selenium/person/day (Yang et al. 1983). Assuming a weight of 55 kg for Chinese men (Yang 1989b), these dietary levels represent 0.027 mg selenium/kg/day and 0.09 mg selenium/kg/day, respectively. In another high selenium area, no neurological effects were observed in individuals who consumed up to 1.51 mg selenium/day (0.027 mg/kg/day) (Yang et al. 1983). Danish

geriatric patients with a mean age of 75.3 years were given daily either a placebo or an antioxidant cocktail containing 0.004 mg/kg/day of selenium as L-selenomethionine along with zinc, vitamins C, A, B6, and E, and gamma-linolenic acid. After 1 year, whole blood selenium concentrations increased in the treated group, and slight but significant improvements in psychological scores were observed (Clausen et al. 1989). Because a mixture of nutrients was administered, the improvement in the patients cannot be attributed to selenium. People living on ranches with high selenium soils where selenium toxicity in livestock had historically been observed were compared to randomly selected residents in Wyoming and South Dakota. Daily selenium intake was measured by analysis of duplicate food portions. Subjects received a complete physical exam with a symptom questionnaire and laboratory tests. There were no biologically significant changes in clinical signs or blood chemistry. Calculated doses ranged from 0.001 to 0.01 mg selenium/kg/day in the diet (Longnecker et al. 1991).

An increased incidence (4 observed cases, 0.97 expected, standardized incidence ratio = 4.14, 95% confidence interval [CI]=1.13–10.60) of amyotrophic lateral sclerosis, a human motor neuron disease of unknown origin, was reported for a cohort of 5,182 residents of Reggio Emilia, Italy who had been exposed to drinking water with high selenium content (7 µg/L) from 1972 to 1988 compared with the incidence among residents of the surrounding area who had received municipal water containing <1 µg/L selenium (Vinceti et al. 1996). A subcohort of 2,065 if these individuals who had been exposed from 1974 (the earliest date for which a chemical analysis of the municipal tap water was available) was also examined and found to have an increased incidence ratio (4 observed cases, 0.47 expected, standardized incidence ratio = 8.59, 95% CI=2.34–21.98).

In a 30-day study of the administration of L-selenomethionine to long-tailed macaques, severe hypothermia was observed in two of five animals administered 0.12 mg selenium/kg/day, but not in any of the eight animals receiving #0.08 mg selenium/kg/day (Cukierski et al. 1989). However, the increased incidence of hypothermia was not statistically significant. Following 1 week of treatment, all animals administered L-selenomethionine, including the two macaques treated with 0.01 mg selenium/kg/day, exhibited increased drowsiness and lethargy (Cukierski et al. 1989).

Symmetrical focal poliomyelomalacia and other forms of paralysis were seen in swine exposed to 0.58–2.1 mg selenium/kg/day after both acute and intermediate exposures (Baker et al. 1989; Goehring et al. 1984; Harrison et al. 1983; Mihailovic et al. 1992; Panter et al. 1996; Penrith and Robinson 1996; Stowe et al. 1992; Wilson et al. 1983, 1988, 1989). This lesion was noted in animals that showed ataxia, inability to stand, and paralysis of the hind limbs. Additionally, bilateral lesions were noted in the ventral

horns of the cervical and lumbar/sacral intumescences of the spinal cord. Necrosis and cavitation were evident in the larger lesions (Harrison et al. 1983). Bilateral lesions were also observed in several nuclei of the brain stem and in the reticular formation (Wilson et al. 1983). Wilson et al. (1983) reproduced the syndrome in growing pigs by feeding them sodium selenite at 50 mg selenium/kg in the diet for 20–40 days. The study authors did not provide sufficient information to calculate doses on a mg selenium/kg body weight basis, but assuming that young swine consume approximately 4% of their body weight each day, this dose was approximately 2.1 mg/kg/day.

In a study of weaned 5-week-old pigs, a dose of 1.3 mg selenium/kg/day given as sodium selenite in capsules killed all eight pigs within 10 days. Histopathological lesions were found in the brain and spinal cord (Wilson et al. 1989). In a study in which pigs were fed 1.25 mg selenium/kg/day in the form of *A. bisulcatus*, D,L-selenomethionine, or selenate, the selenium in *A. bisulcatus* was the most potent neurotoxin, resulting in complete paralysis in four of five pigs after 5 days of treatment, and in the last pig after 3 weeks of treatment (Panter et al. 1996). In pigs fed selenate, three of five developed complete paralysis, and one pig developed posterior paralysis after 4–21 days of treatment. Although D,L-selenomethionine resulted in the greatest incidence of selenosis, it was the least potent neurotoxicant, resulting in posterior paralysis in two of five pigs after 9 and 24 days of treatment; the pigs that did not develop paralysis were fed D,L-selenomethionine for approximately 31 days. The form of selenium in *A. bisulcatus* is unknown, although Panter et al. (1996) indicate that it is nonprotein.

It has long been believed that blind staggers in livestock results from consumption of plants high in selenium (100–10,000 mg selenium/kg plant) (Rosenfeld and Beath 1964). These plants, which include *A. bisulcatus*, are known as selenium-indicator plants. Blind staggers is characterized by impaired vision, aimless wandering behavior, reduced consumption of food and water, and finally paralysis and death (Rosenfeld and Beath 1964; Shamberger 1986). Trembling of the skeletal muscles was observed in steers fed sodium selenite mixed in the feed at doses between 0.6 and 1.1 mg selenium/kg/day (Maag et al. 1960). At necropsy, two of six steers exhibited neuronal degeneration of the cerebral and cerebellar cortices. However, more recent studies in which cattle were treated with known amounts of selenium have not replicated these effects , and it is likely that blind staggers is not solely the result of selenium toxicity, but may also be attributable to other unidentified causes. For example, treatment of 20 steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days produced symptoms of selenosis (hoof lesions), but did not produce any neurological signs associated with blind staggers and did not produce any treatment-related changes in the histology of the central nervous system (O'Toole and Raisbeck 1995).

Neurological effects have also been reported for mice after acute or intermediate exposures to selenium. A single oral dose of selenium dioxide dissolved in water given to mice at $1/10^{th}$ the LD_{50} (1.7 mg/kg) caused moderate reductions in alertness, spontaneous activity, touch response, muscle tone, and respiration. Pentobarbital sleeping time was also significantly increased, and there was moderate hypothermia (Singh and Junnarkar 1991). Brain tissue from male BALB/c mice administered sodium selenite or seleno-L-methionine in drinking water at 0, 1, 3, or 9 ppm selenium (sodium selenite : 0.03, 0.24, 0.58, or 1.34 mg selenium/kg/day; seleno-L-methionine: 0.03, 0.26, 0.63, or 1.96 mg selenium/kg/day) for 14 days was examined for changes in the concentrations of norepinephrine (NE), dopamine (DA), dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), serotonin (5-HT), and 5-hydroxyindolacetic acid (5-HIAA) (Tsunoda et al. 2000). Treatment with seleno-L-methionine produced no significant changes in the concentrations of any of the neurotransmitters or their metabolites. DOPAC, DA, and HVA were increased in the striatum of mice receiving 3 or 9 ppm selenium as selenite. The increase was significant at both concentrations for DOPAC and at 3 ppm (but not 9 ppm) for HVA, but was not significant at either concentration for DA. No changes were observed for levels of NE, 5-HT, or 5-HIAA levels in any brain region of mice treated with sodium selenite.

Exposure of female BALB/c mice to 0.21 mg selenium/kg/day for 6 months from diets containing selenium as sodium selenite resulted in significant changes in behavior during open field testing (Boylan et al. 1990). Open field testing measures the arousal level of small rodents and can differentiate between fear-related behavior and general arousal. Mice receiving excessive selenium had reduced sniffing behavior and exhibited greater activity entering more squares, and more interior squares than mice receiving normal selenium diets. These behaviors are indicative of a general state of arousal rather than fear-motivated activity.

No studies were located concerning neurological effects in humans or experimental animals following oral exposure to selenium sulfide or disulfide.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects following oral exposure to selenium or selenium compounds for each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding adverse effects on human reproduction following oral exposure to elemental selenium or to selenium compounds. No significant correlation was found between the seminal plasma selenium concentration and sperm count or mobility in sperm samples from 211 men (Roy et al. 1990). A nonsignificant increase in spontaneous abortions (relative risk [RR]=1.73; 95% CI=0.62–4.80) was reported among births in the municipality of Reggio Emilia, Italy, where women had been exposed to drinking water containing 7–9 µg selenium (as selenate) between 1972 and 1988 (Vinceti et al. 2000a). A preliminary study completed in China suggests that selenium supplementation (100 µg/day, form not stated) during pregnancy may reduce the incidence of pregnancy-induced hypertension (Li and Shi-mei 1994).

Selenium administered in the diet or in drinking water over short exposure periods (e.g., 1 month) does not appear to affect the fertility of female animals unless the intake is sufficiently high to cause general toxicity (Nobunaga et al. 1979). Despite a small increase in the number of abnormal length estrous cycles, Nobunaga et al. (1979) found no adverse effect on the fertility of female mice from administration of sodium selenite at doses of 0.34 mg selenium/kg/day in drinking water for 30 days before mating and for 18 days during pregnancy. On the other hand, chronic exposure of mice and rats to otherwise nontoxic doses has been shown to reduce fertility and to reduce markedly the viability of the offspring of pairs that are able to conceive (Schroeder and Mitchener 1971b; Wahlstrom and Olson 1959b).

A study of supplementation of female pigs with 0.1 or 0.3 ppm selenium (doses not available) administered as a selenium-enriched yeast or sodium selenite in the diet, from 60 days before breeding until weaning found no adverse effects on reproductive performance (measured by number of offspring) or growth (Mahan and Kim 1996). In another study of the effect of selenium on fertility in pigs, females fed sodium selenite at 0.4 mg selenium/kg/day from 8 weeks of age exhibited reduced rates of conception and also produced offspring with significantly reduced birth weight and weaning weights in the first and second litters (Wahlstrom and Olson 1959b). An altered menstrual cycle was reported in monkeys administered 0.08 mg selenium/kg/day as L-selenomethionine for 30 days (Cukierski et al. 1989).

Vaginal cytology of female rats provided with drinking water containing selenate or selenite indicated that the rats spent more time in diestrus and less time in proestrus and estrus than the controls (NTP 1994). This effect occurred following treatment with 0.31 mg selenium/kg/day as selenate or 0.86 mg selenium/kg/day as selenite. The animals in these studies were not mated, so it is not known if the effects

on the estrous cycle had any effect on fertility. Effects on the estrous cycle were not observed in mice treated with selenate or selenite in the drinking water at doses up to 7.17 mg selenium/kg/day for selenate, or at doses up to 3.83 selenium/kg/day for selenite (NTP 1994).

In a three-generation reproduction study, selenium administered as sodium selenate (0.57 mg selenium/kg/day) in the drinking water of breeding mice produced adverse effects on reproduction (Schroeder and Mitchener 1971b). The most notable observed effects included the failure of about half of the F3 generation pairs to breed successfully. In a two-generation study using rats, selenium administered as potassium selenate had no effect on reproduction at a dose of 0.21 mg selenium/kg/day for 1 year; however, decreased fertility and pup survival were noted at 1.05 mg selenium/kg/day (Rosenfeld and Beath 1954). At 0.35 mg selenium/kg/day for 1 year, the number of young successfully reared by the females was reduced by 50%, and the body weight of the females was approximately 20% less than that of the control females (Rosenfeld and Beath 1954).

A short-term reproductive study of the effects of sodium selenate in drinking water on rats reported some female reproductive toxicity (reduced corpora lutea, reduced implants per litter, shorter estrous cycle), but only at doses (0.418 mg selenium/kg/day) that produced signs of severe maternal toxicity, including a large reduction in water consumption (NTP 1996).

Data from animal studies suggest that exposure to excessive selenium has adverse effects on testosterone levels and sperm production and increases the percentage of abnormal sperm (El-Zarkouny et al. 1999; Kaur and Parshad 1994; NTP 1994). A significant reduction (49%) in serum testosterone levels was reported for New Zealand White rabbits gavaged with 0.3 mg selenium/kg (0.001 mg selenium/kg/day) as sodium selenite once a week for 6 weeks (El-Zarkouny et al. 1999). The percentage of spermatozoa without an acrosome was also increased in treated rabbits compared with controls, but the difference was not significant. Sperm motility, ejaculate volume, sperm concentration, and total sperm output were all reduced by selenium treatment, but statistical analysis of these data was not presented.

Exposure of Wistar rats to 0.234 mg selenium/kg/day as sodium selenite in water produced testicular hypertrophy (Turan et al. 1999a). A dose-related increase in abnormal sperm and a decrease in live sperm were observed in wild-caught rats exposed to selenite in the diet at 0.1 and 0.2 mg selenium/kg/day (Kaur and Parshad 1994). The percentage of abnormal sperm was 3.9% at 0.1 mg/kg/day and 24.6% at 0.2 mg/kg/day. The abnormalities observed were principally in the midpiece region of the sperm, the region that contains a selenoprotein (Sunde 1990). Decreased sperm counts were observed in rats

provided with selenate or selenite in drinking water for 13 weeks at a dose of 0.29 mg selenium/kg/day for selenate and a dose of 0.17 mg selenium/kg/day for selenite (NTP 1994). Effects on sperm were not observed in mice treated with selenate or selenite in the drinking water at doses up to 5.45 mg selenium/kg/day for selenate, and at doses up to 3.31 mg selenium/kg/day for selenite (NTP 1994). The administration of 1.05 mg selenium/kg/day as potassium selenate to rats in drinking water for 1 year did not affect male fertility (Rosenfeld and Beath 1954), and the administration of 0.57 mg selenium/kg/day as sodium selenate for three generations did not reduce male fertility in mice (Schroeder and Mitchener 1971b). A short-term reproductive study of the effects of sodium selenate in drinking water on rats at doses (0.418 mg selenium/kg/day) that produced signs of systemic toxicity did not cause any increase in sperm abnormalities or lesions of the testis or epididymis (NTP 1996).

In a review of selenium poisoning in domestic animals, Harr and Muth (1972) noted a decreased conception rate and an increased fetal resorption rate in cattle, sheep, and horses fed diets naturally containing organic selenium compounds at 25–50 mg selenium/kg diet. Assuming that large animals consume an amount of food equal to about 2–3% of their body weight daily, the doses would have been approximately 0.5–1.5 mg selenium/kg/day. These levels of selenium also produced other signs of toxicity, including hair loss, lameness, and degeneration and fibrosis of the heart, liver, and kidneys. In a case control study of 136 Holstein cows from four herds, an association of cystic ovaries with blood selenium concentrations greater than 108 ng/mL was found (Mohammed et al. 1991). The concentration of progesterone in the milk was significantly higher in the controls than in the cows receiving selenium supplementation, but no information on the selenium dose was presented. No change in estrus cycle length, estrus behavior, progesterone, or estrogen profiles or pregnancy rate was observed in a study of the reproductive response of ewes fed alfalfa pellets containing sodium selenate (24 ppm selenium) or *A. bisculcatus* (29 ppm selenium) as a selenium source for 88 days, from >52 days before pregnancy up to day 28 of gestation (Panter et al. 1995). Doses could not be calculated as food consumption was not listed, and the paper states that the food supply was limited to match that of the group with the lowest intake.

The highest NOAEL value for reproductive effects following intermediate oral exposure to sodium selenite and all reliable LOAEL values for reproductive effects following intermediate or chronic oral exposure to selenium compounds other than selenium sulfide are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies have demonstrated that selenium or its compounds are teratogenic in humans. Robertson (1970) reported on the outcome of pregnancies in a laboratory in which workers handled sodium selenite. Of the five pregnancies, four ended in spontaneous abortion and one resulted in an infant with bilateral clubfoot. The urinary selenium levels in all subjects were similar to those in other individuals living in the same area. The limited number of cases, possible exposure to other toxic agents, and other confounding factors leave the relationship between sodium selenite and developmental effects inconclusive.

No significant increase in spontaneous abortions (RR=1.73; 95% CI=0.62–4.80) was reported among births in the municipality of Reggio Emilia, Italy, where women had been exposed to drinking water containing 7–9 µg selenium (as selenate) between 1972 and 1988 (Vinceti et al. 2000a). Body weight and length at birth were similar in infants of exposed and unexposed women, and no significant increase in the prevalence of congenital abnormalities was found for 353 infants of exposed mothers compared with the 14,481 births among unexposed women.

Zierler et al. (1988) performed a case control study of 270 children born in Massachusetts with severe congenital heart disease and 665 controls randomly selected from birth certificates. The study compared the selenium concentrations in the public drinking water supply used by the mothers close to the time of conception to the selenium concentrations in the water consumed by the controls. The results indicated that selenium exposure via drinking water was associated with a reduction in the risk of congenital heart defects (cono-truncal defects, venticular septal defects, coarctation of the aorta, and patent ductus arteriosis), but many variables are unknown, including other possible confounders (no adjustment for age, parity, tobacco, alcohol, drug use, or socioeconomic status), other sources of selenium in the mothers' diet and environment, the amount of drinking water consumed, and the selenium concentrations in the water during the first trimester.

Excess selenium is a demonstrated teratogen in birds. However, there is no clear evidence linking selenium exposures to teratogenic effects in mammals. Several studies have documented the sensitivity of chick embryos to selenium poisoning. Hatchability of eggs is reduced by dietary levels of organic selenium in grain that are too low to cause toxicity in other farm animals. The eggs are fertile but often produce grossly deformed embryos lacking eyes and beaks and having deformed wings and feet (Franke and Tully 1935; Franke et al. 1936; Gruenwald 1958; Palmer et al. 1973). Deformed embryos have also

been produced by injection of aqueous sodium selenite or sodium selenate into the air cell of the normal, fertile eggs of chickens (Franke et al. 1936; Khan and Gilani 1980). The incidence of malformation among coot, duck, stilt, and grebe embryos from eggs of birds ingesting plant and other food from irrigation drainwater ponds in the San Joaquin Valley of California was much higher than expected (10–42%, depending on the species, versus less than 1% based on data from other areas) (Ohlendorf et al. 1986a, 1988). Selenium concentrations in these ponds were greater than 0.3 mg/L.

The consumption of naturally high seleniferous diets by sheep (Rosenfeld and Beath 1964) and cattle (Dinkel et al. 1963) may interfere with normal fetal development and produce malformations. Malformations were associated with alkali disease and occurred at dietary levels that produced other toxic manifestations, but it is not clear if these reports took into account consumption of other toxic range plants. The specific selenium compound or compounds possibly associated with livestock developmental toxicity have not been identified. No change in the outcome of pregnancy was observed in a study of the reproductive response of ewes fed alfalfa pellets containing sodium selenate (24 ppm selenium) or *Astragalus bisculcatus* (29 ppm selenium) as a selenium source for 88 days, from >52 days before pregnancy up to day 28 of gestation (Panter et al. 1995). All lambs appeared normal; and there was no significant difference in the number or weight of lambs born to treated and control ewes. Doses could not be calculated, as food consumption was not listed, and the paper states that the food supply was limited to match that of the group with the lowest intake

In an intermediate-duration study, an increased number of deaths between birth and weaning, reduced birth weight, and reduced body weight at weaning were observed in offspring of pigs fed selenite at 0.4 mg/kg/day for an unstated period of time (Wahlstrom and Olson 1959b). Treatment of 15 pregnant cows with diets containing 0.25 (control), 6, or 12 ppm selenium (0.005, 0.135, or 0.265 mg Se/kg/day) as sodium selenite beginning at 80 to 110 days gestation and continuing for 3 months resulted in no abnormalities among the offspring apart from one calf in the 12 ppm group which was born weak and subsequently died (Yaeger et al. 1998). This calf had myocardial lesions similar to those described for selenium toxicosis and had markedly elevated hepatic selenium levels, although selenium levels in blood and hair of this calf and its dam were lower than average for the 12 ppm group.

In studies of laboratory mammals, the administration of inorganic selenium compounds at levels that are not maternally toxic has not produced terata (Bergman et al. 1990; Chiachun et al. 1991; Ferm et al. 1990; NTP 1996; Poulsen et al. 1989; Rosenfeld and Beath 1954; Schroeder and Mitchener 1971b; Thorlacius-Ussing 1990). Ferm et al. (1990) administered a single dose of sodium selenate, sodium selenite, or

L-selenomethionine (0, 1.8, 2.2, 2.7, 4.0, 5.0, or 5.9 mg selenium/kg/day) to pregnant Syrian hamsters on gestation day 8. Pathological examination of the fetuses on day 13 showed that the percentage of abnormal litters was significantly increased at a dose of 2.7 mg/kg and greater. Encephalocele was the major malformation noted, and incidences were as follows: 0/71 controls; 4/55 (7.3%) at 1.8 mg/kg; 1/49 (2%) at 2.2 mg/kg; 7/66 (10.6%) at 2.7 mg/kg; 15/70 (21.4%) at 4 mg/kg; 9/38 (23.7%) at 5 mg/kg; and 6/16 (37.5%) at 5.9 mg/kg. Nobunaga et al. (1979) found that administration of sodium selenite in drinking water at 0.34 mg selenium/kg/day for 30 days before mating and for 18 days during pregnancy slightly, but significantly, reduced fetal growth in mice. However, there was no effect on fetal growth in the same study at a dose of 0.17 mg selenium/kg/day. A short-term developmental study (from gestation day 6 until birth) of the effects of sodium selenate in drinking water on rats produced some developmental toxicity (decreased number of live births, reduced pup weight, increased gestation period), but only at doses (0.418 mg selenium/kg/day) that produced signs of severe maternal toxicity including a large reduction in water consumption (NTP 1996). Selenium administered as potassium selenate in drinking water to male and female rats at a dose of 1.05 mg selenium/kg/day for 1–8 months for two successive generations did not cause congenital malformations (Rosenfeld and Beath 1954). Similarly, administration of 0.57 mg selenium/kg/day as sodium selenate in the drinking water of breeding mice for three generations did not have teratogenic effects, although there was an increased incidence in fetal deaths, and a high proportion of the surviving offspring were runts (Schroeder and Mitchener 1971b).

Poulsen et al. (1989) demonstrated that pigs exposed to 42.4 mg/day of selenium as sodium selenite in feed throughout pregnancy produced normal litters, with no adverse effect on piglet survival, litter size, or body weight at birth. Body weights of the pigs during pregnancy were not provided, and therefore mg/kg/day doses could not be calculated. Body weight gains of pigs fed selenium as selenite at a dose of 0.4 mg selenium/kg/day after weaning (duration not specified) were reduced (Wahlstrom and Olson 1959a). The reduction in body weight gain was greater among pigs from dams not fed selenium during gestation and lactation compared to pigs fed selenium (0.4 mg/kg/day) during gestation and lactation. Without providing data, the study authors indicated that there was a greater loss of pigs at birth and during lactation from sows fed selenium, which may have eliminated susceptible pigs.

In a teratology study of long-tailed macaques, no gross abnormalities or growth retardations were observed in fetuses from mothers administered L-selenomethionine at levels of 0.003, 0.025, 0.15, or 0.30 mg selenium/kg/day on gestational days 20–50 (10 animals per group); the mid and high doses were maternally toxic (Tarantal et al. 1991).

The highest NOAEL value and all reliable LOAEL values for developmental effects following intermediate or chronic oral exposure to selenium compounds are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

Early studies reporting that selenium was carcinogenic in mammals after being provided as seleniferous corn or wheat in the diet (Nelson et al. 1943), as sodium selenite or sodium selenate in drinking water (Schroeder and Mitchener 1971a), or as sodium selenate in the diet (Volgarev and Tscherkes 1967) were flawed. The majority of subsequent studies of humans and animals have revealed either no association between selenium intake and the incidence of cancer (Azin et al. 1998; Beems 1986; Coates et al. 1988; Harr et al. 1967; Ma et al. 1995; Menkes et al. 1986; Ratnasinghe et al. 2000; Thompson and Becci 1979; Viacetti et al. 1995; Virtamo et al. 1987) or a chemopreventive association (Birt et al. 1982; Clark et al. 1996a, 1999; Finley et al. 2000; Ip 1981, 1983; Ip and Lisk 1995; Ip et al. 1996, 1997, 1998, 2000a, 2000b; Jiang et al. 1999; Ma et al. 1995; Medina and Shepherd 1981; Overvad et al. 1985; Schrauzer et al. 1976, 1977; Shamberger et al. 1976; Soullier et al. 1981; Thompson and Becci 1980; Woutersen et al. 1999; Yoshizawa et al. 1998).

The only selenium compound that has been shown to be carcinogenic in animals is selenium sulfide (NTP 1980c), although there is also some evidence for carcinogenicity due to ethyl selenac (Innes et al. 1969; NCI 1968). These compounds are very different chemically from the organic and inorganic forms found in foods and the environment. Human dietary studies generally do not identify the selenium form specifically; both organic (from grains and other plant and animal products) and inorganic (from drinking water) forms are ingested. Animal bioassays in which selenium was administered as sodium selenate, sodium selenite, or organic forms of selenium have all shown similar negative results.

Excess incidence of melanoma was reported for a cohort of 2,065 individuals exposed to selenium as selenate that contaminated the municipal water supply in Reggio Emilia, Italy from 1972 until 1988 (Vinceti et al. 1998). Eight individuals among the exposed cohort developed melanoma compared with 128 in the remainder of the municipal population (total number of individuals not given). The SMRs were 5.0 (95% CI=1.6–12.0) for males and 3.2 (95% CI=1.0–7.7) for females. The authors estimate the general dietary intake of selenium in the area to be 45–50 µg/day and the excess selenium supplied in the contaminated tap water to be 10–20 µg/day. However, the study is limited by the fact that no individual

measurements of selenium exposure were made, and individuals were classed as exposed or unexposed depending on their place of residence.

A study of the effects of nutritional supplementation with selenium found a significant reduction in overall cancer mortality and in the incidence of lung (RR=0.54, 95% CI=0.3–0.98, P=0.04), colorectal (RR=0.42, 95% CI=0.18–0.95, P=0.03), and prostate (RR=0.37, 95% CI=0.18–0.71, P=0.003) cancer (Clark et al. 1996a, 1999). The original intent of the study was to assess the effects of selenium supplementation on nonmelanoma skin cancer. Patients with a history of skin carcinoma (1,312 individuals) were randomized into two groups; one group received a selenium supplement of 200 µg/day, and the other received a placebo. Groups were treated for an average of 4.5 years and followed for an average of 6.5 years. Supplementation produced no difference in skin cancer incidence; however, secondary end point analyses of the data found a protective effect for selenium for the cancers described above.

Supporting evidence for an antiprostate cancer effect of selenium was obtained for a nested case-control design within the Health Professional Follow-up study (Yoshizawa et al. 1998), which found that higher prediagnostic selenium levels were associated with reduced prostate cancer incidence. This study included 33,737 male health professionals aged 40–75 years who provided toenail clippings in 1987. The cohort was assessed by questionnaire for incidence of new cases of prostate cancer from 1989 to 1994. Higher levels of selenium in toenail clippings were significantly associated with a reduced risk of prostate cancer. After controlling for factors such as a family history of prostate cancer, body mass index, calcium intake, lycopene intake, saturated fat intake, vasectomy, and geographical region, the odds ratio (OR) was 0.35 (95% CI=0.16–0.78, P for trend=0.03).

Epidemiological studies that focused on the selenium concentration of forage crops as an indicator of available dietary selenium indicated an inverse association between selenium levels and cancer occurrence, with few exceptions. In the United States, male mortality due to cancer of the tongue, esophagus, stomach, intestine, rectum, liver, pancreas, larynx, lungs, kidneys, and bladder was significantly lower in states with high selenium levels in forage crops (concentrations in excess of 0.10 mg selenium/kg) (Shamberger et al. 1976). For females in states with high selenium levels, significantly lower cancer death rates were found for cancer of the esophagus, stomach, intestine, rectum, liver, pancreas, lungs, bladder, thyroid, breast, and uterus (Shamberger et al. 1976). Only male and female mortality due to cancer of the skin and eye, male mortality due to cancer of the lip and aleukemia (absence or deficiency of leukocytes in the blood), and female mortality due to dermal melanoma were

associated with high selenium levels in forage crops. Many of the high selenium areas are in the southwestern portion of the United States, and therefore, exposures to ultraviolet light may have contributed to the skin cancers observed in these areas (Shamberger et al. 1976). In a comparison of selenium intake and cancer mortality rates in different countries, Schrauzer et al. (1977) detected a cancer chemopreventive association between the selenium content of the diet and age-corrected cancer mortality from leukemia and cancers of the intestine, rectum, breast, ovary, prostate, lung, pancreas, skin, and bladder.

In a case control study of lung cancer patients, Menkes et al. (1986) found that the risk of lung cancer was not associated with serum selenium levels (0.113 and 0.110 mg selenium/L in cases and controls, respectively), but significantly increased with decreasing serum levels of vitamins A and E. The study authors suggested that high serum selenium levels were significantly associated with an increased incidence of squamous cell carcinoma as compared to other cellular tumor types, but the statistical analysis used was flawed. In a region of China with high rates of stomach cancer and low intake of several micronutrients (selenium not specifically stated), an intervention trial in 29,584 adults for 5.25 years demonstrated a 21% decrease in stomach cancer in the randomly selected group receiving a nutritional supplement of beta carotene (15 mg/day), vitamin E (30 mg/day), and selenium (50 µg selenium/day as selenium yeast) (Blot et al. 1993). However, because the three nutrients were given in combination, it is not possible to determine what part of this effect (if any) was due to selenium.

Low serum selenium levels have been associated with an increased incidence of cancer in some prospective epidemiological studies (Salonen et al. 1984, 1985; Willet et al. 1983). In the United States, Willet et al. (1983) found that the risk of cancer for subjects in the lowest quintile (fifth) of serum selenium concentrations (<0.115 mg selenium/L) was twice that of subjects in the highest quintile (>0.154 mg selenium/L). In Finland, Salonen et al. (1985) found the risk of fatal cancer for subjects in the lowest tertile (third) of serum selenium concentrations (<0.047 mg selenium/L) was 5.8 times higher than that of the remaining subjects. Mean serum selenium levels in Americans (0.129 mg selenium/L cases; 0.136 mg selenium/L controls) (Willett et al. 1983) are more than twice the mean serum selenium levels in the Finns (0.0505 mg selenium/L for cases; 0.0543 mg selenium/L for controls) (Salonen et al. 1984). Although the age-specific risk of fatal cancers in the two populations cannot be calculated from the data reported, the overall incidence of cancer in the 4-year Finnish study was less than half that in the 5-year U.S. study. In addition, other prospective studies of Americans have found no correlation between fatal cancer and blood selenium concentrations (Coates et al. 1988). Thus, one cannot predict relative cancer risks with serum selenium levels in one population based on data from another population.

A 9-year prospective follow-up study was conducted by Virtamo et al. (1987) on a group of men in Finland. At the beginning of the study, blood samples were taken as part of a study of coronary heart disease and other atherosclerotic diseases. Cancer data were collected from central registries for the years 1976 through 1983. The results indicated no association between low serum selenium levels (<0.045 mg selenium/L) and an increased risk of cancer. Evidence suggests that combined dietary deficiencies of vitamin E and selenium may be associated with increased cancer risk (Salonen et al. 1985).

Epidemiological studies of breast cancer have found inverse correlations, positive correlations, and no correlations between tissue selenium concentrations and cancer incidence (recently reviewed by Garland et al. 1993). In a case control study of plasma selenium and breast cancer in which the controls had benign breast disease, a preventive effect of selenium was found only among individuals who had higher plasma selenium and were not taking selenium supplementation (Hardell et al. 1993). This effect was significant (odds ratio 0.38) at a serum selenium concentration range of 0.08–0.09 mg/L in women 50 years old or more. GSH-Px activity in erythrocytes was not found to be a marker for the risk of breast cancer. A case control study of 162 cases of breast cancer in Dutch women did not find a significant difference in dietary, plasma, erythrocyte, or toenail selenium between cases and 529 controls when multivariate-adjusted odds ratios were calculated. Dutch women have lower selenium intake than women in the United States and one of the highest incidences of breast cancer in Western Europe. The authors of this study surmised that other studies reporting an inverse relationship between selenium levels and breast cancer may be seeing an effect of the cancer (e.g., decreased uptake of selenium or anorexia), rather than lower selenium level contributing to the development of cancer (van't Veer et al. 1990). Similarly, a large prospective study of 434 cases in the United States found no correlation between selenium content in nails, established as a long-term marker of selenium (Hunter et al. 1990a), and breast cancer (Hunter et al. 1990b). It is interesting to note that a more recent investigation of the same cancer cases found an inverse correlation between vitamin A (retinoids) in the diet and breast cancer (Hunter et al. 1993). Retinoids are believed to have chemopreventive activity (Clausen et al. 1989; Hunter at al. 1993). Although the data as a whole for breast cancer and tissue selenium concentrations do not support a clear chemopreventive effect for selenium, it is possible that very high selenium concentrations or very low selenium concentrations outside the ranges observed in these studies could play a role in human cancer risk (Garland et al. 1993).

There were several inadequacies in the early studies that reported carcinogenic effects in animals following oral administration of selenium-containing compounds. Nelson et al. (1943) (also reported as Fitzhugh et al. 1944) administered naturally seleniferous corn or wheat diets containing 5, 7, or 10 mg

selenium/kg diet (0.25, 0.35, or 0.50 mg selenium/kg/day) to female rats for 2 years. Selenium administration produced high mortality (69%) in all treatment groups by the end of the first 12 months, and the first tumors appeared after 18 months of treatment. Tumors developed only in animals with cirrhotic livers, and the tumors were reported to be nonmalignant. The possible contribution of overt hepatotoxicity to the development of liver tumors is not known. The incidences of tumors in the surviving animals in the three dose groups were 6/25, 3/21, and 2/7, respectively. The investigators had difficulty discerning malignant from nonmalignant tumors, and most animals had died of cirrhosis of the liver before the appearance of liver tumors. These difficulties cast doubt on the conclusion of the investigators that selenium induced tumor formation in these rats.

A statistically significant increase was reported in the incidence of all tumors and malignant tumors in rats administered 0.28–0.42 mg selenium/kg/day as sodium selenite or sodium selenate in drinking water for a lifetime (Schroeder and Mitchener 1971a). Not all autopsied animals were examined histologically, however, and high mortality in all groups occurred as a result of a virulent pneumonia epidemic that occurred during the study. In addition, the statistical analysis failed to account for the fact that the selenium-treated rats lived longer than did the control rats. Analysis of the incidence of tumors among animals with equal longevities indicates that the incidence of tumors in the selenate-treated rats was not significantly different from that in the controls.

A series of dietary studies assessed the effects of various dietary supplements on selenium tumor induction in male rats (Volgarev and Tscherkes 1967), but the conclusions that can be drawn from these experiments are limited since they did not include controls. Tumors (primarily liver) were found in 10/23 male rats administered sodium selenate in the diet at a dose of 0.34 mg selenium/kg/day for more than 18 months (Volgarev and Tscherkes 1967). The first tumors appeared after 18 months of selenium administration, by which time, 43% of the animals had already died (group started with 40 animals). Tumors were also found in 3/16 male rats administered sodium selenate in the diet at an initial dose of 0.34 mg selenium/kg/day for 6 months, followed by 0.68 mg/kg/day until the animals death (Volgarev and Tscherkes 1967). In a third group of experiments, no tumors were found in 200 male rats administered sodium selenate in the diet (0.34 mg selenium/kg/day) for 26 months. However, there was very high mortality among these rats, and survival time was 10 months shorter than among the similarly fed animals in the first experiment. The authors noted that an additional 200 male rats were maintained in their laboratory during these experiments and fed stock rations. The life spans of these animals exceeded those used in the experiments and no tumors were found at autopsy.

More recent animal bioassays have failed to demonstrate any association between excessive selenium exposure and carcinogenesis. Chen et al. (2000) reported a significant increase in rat esophageal adenocarcinogenesis in response to supplementation with 0.06 mg selenium/kg/day as sodium selenite for 40 weeks. However, selenium supplementation has generally been shown to significantly inhibit tumors induced by chemicals, viruses, or ultraviolet light (Birt et al. 1982; Finley et al. 2000; Ip 1981, 1983; Ip and Lisk 1995; Ip et al. 1996, 1997,1998, 2000a, 2000b; Jabobs 1983; Jacobs et al. 1977a, 1977b, 1979, 1981; Jiang et al. 1999; Medina and Shepherd 1981; Overvad et al. 1985; Schrauzer et al. 1976; Soullier et al. 1981; Thompson and Becci 1980; Woutersen et al. 1999). Results following administration of selenium as sodium selenate, sodium selenite, and organic forms of selenium are similar. Additional research reviewed in El-Bayoumy (1991, 1995, 1997) indicates that synthetic organoselenium compounds may be more potent cancer preventive agents than selenate, selenite, or the selenoamino acids.

Two sources reported the results of a study of rats administered sodium selenate or sodium selenite in the diet for a lifetime (Harr et al. 1967; Tinsley et al. 1967). A vehicle control and two positive control groups (administered a known hepatocarcinogen, *N*-2-fluorenyl-acetamide [FAA]) were included. Mortality was high in the highest dose group (0.8 mg selenium/kg/day), and therefore, selenium administration was discontinued. Longevity was reduced in animals fed 0.4 mg selenium/kg/day, but not in the animals administered lower doses. Of the original 1,437 experimental animals, 1,126 were necropsied. Half of the 88 FAA-fed rats developed neoplasms, half of which were hepatic carcinomas, indicating that the strain of rat and dietary conditions were compatible with the development of hepatic carcinogenesis. The incidence of cancer of all types in the necropsied control rats (11 out of 482, or 2.3%) was somewhat higher than the incidence of cancer in the selenium-treated animals that were necropsied (9 out of 553, or 1.6%). A statistical analysis of the data from this study was not reported. Although the reduced longevity of animals administered 0.4 mg selenium/kg/day might have prevented the observation of some late-developing cancers, the large number of rats necropsied, the end points examined, and the doses administered provide credible evidence of the lack of carcinogenic potential of sodium selenate or selenite.

Mice were fed tortula yeast diets containing up to 1.0 mg selenium/kg diet (equivalent to 0.13 mg selenium/kg body weight/day) as sodium selenite for 2 weeks prior to a single application of 0.125 mg 7,12-dimethylbenz[a]anthracene (DMBA) to the skin or repeated daily applications of 0.25 mL of a 0.03% solution of benzo[a]pyrene in acetone for 27 weeks (Shamberger 1970). The highest dose of selenite used, 0.13 mg selenium/kg/day, significantly decreased the number of tumors induced by both aromatic compounds. No significant increase was found in the incidence of spontaneous tumors in mice

following administration of 3 mg selenium/L in drinking water as either sodium selenite or sodium selenate for a lifetime (Schroeder and Mitchener 1972). This level corresponds to doses of 0.31–0.34 mg selenium/kg/day for the males and 0.42 mg selenium/kg/day for the females. The single dose administered, however, might not have been the maximal dose that could be tolerated. There were 7% more malignant tumors in the selenium-treated animals (13 out of 88 sectioned, or 15%) than in the controls (10 out of 119 sectioned, or 8%), but the difference was not statistically significant. The forms of selenium administered did not influence the incidence of tumors. In this study, only 88 out of 211 selenium-treated animals and 109 out of 209 control animals were examined histologically.

The only selenium compound that has been shown to be carcinogenic in animals is selenium sulfide (NTP 1980c), although there is some inconclusive evidence that ethyl selenac may also be carcinogenic (Innes et al. 1969; NCI 1968). A statistically significant increase in hepatomas (0/16 controls; 12/16 treated) was observed in male mice of one strain (C57BL/6 x C3H/Anf)F_1) receiving 2 mg selenium/kg as ethyl selenac, but not in male or female mice of another strain (C57BL/6 x AKR)F_1) receiving the same dose (Innes et al. 1969; NCI 1968).

Statistically significant increases in hepatocellular carcinomas and adenomas in rats and hepatic carcinomas and adenomas, as well as alveolar/bronchiolar carcinomas and adenomas, in female mice have been observed following chronic oral exposure to selenium sulfide (NTP 1980c). The incidence of hepatocellular carcinomas in rats was 1/50, 0/50, and 15/49 in males and 0/50, 0/50, and 21/50 in females at 0, 3, and 15 mg selenium sulfide/kg/day, respectively. In mice, the incidences of hepatocellular carcinomas and adenomas were 15/50, 14/50, and 23/50 in males, and 0/49, 2/50, and 25/49 in females at 0, 20, and 100 mg selenium sulfide/kg/day, respectively. Selenium sulfide is a pharmaceutical compound used in some antidandruff shampoos and is not administered orally. Because selenium sulfide is not absorbed through the skin, use of shampoos containing this compound should be safe, unless one intentionally consumes the product or has open cuts or sores on the scalp or hands. Chemically, selenium sulfide and ethyl selenac are very different from the organic and inorganic selenium compounds found in foods and in the environment.

In 1975, the International Agency for Research on Cancer (IARC) evaluated the literature relating selenium to carcinogenesis in both humans and animals. The Agency stated that the available data provided no suggestion that selenium is carcinogenic in humans (IARC 1975a), and IARC subsequently assigned selenium to Group 3: not classifiable as to its carcinogenicity to humans (IARC 1987). The forms of selenium considered included sodium selenate, sodium selenite, and the organic forms of

selenium contained in plant materials. Separate evaluations of ethyl selenac and methyl selenac assigned them to group 3, also (IARC 1975a, 1987). According to EPA, selenium is not classifiable as to its carcinogenicity in humans and is rated as Group D (IRIS 2001). The evidence for selenium sulfide, however, is sufficient to classify it as group B2 (probable human carcinogen)(IRIS 2001).

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located concerning death in humans after dermal exposure to selenium or selenium compounds. In a range-finding study using mice dermally exposed to selenium sulfide for a maximum of 17 applications, 8 out of 20 animals died at 714 mg selenium sulfide/kg (NTP 1980a). However, the effects noted in this study were equivocal since there was no indication that the application sites were covered to prevent ingestion. Further, severe skin damage developed, and this may have led to direct systemic absorption of the compound.

3.2.3.2 Systemic Effects

No studies were located concerning respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, or body weight effects in humans or other animals following dermal exposure to selenium or selenium compounds.

Dermal Effects. Skin toxicity in humans, notably skin rashes, burns, and contact dermatitis, has been reported for both acute and chronic exposure to selenium fumes and acute exposures to selenium dioxide (Middleton 1947). No effects were detected in a study of eight women exposed daily for 2 weeks to an experimental sunscreen lotion containing up to 0.003 mg/kg/day selenium as L-selenomethionine (Burke et al. 1992a). A case report of a severe allergic skin response following intermediate exposure to sodium selenite (Senff et al. 1988) is discussed under immunological effects. Single topical exposures to selenious acid resulted in purpura, inflammation around hair follicles, and a pustular rash with some ulceration in exposed workers (Pringle 1942). However, these effects may have been due to the caustic effects of the acid. A single case report of hyperpigmentation and hair loss after use of a shampoo containing 1% selenium sulfide was located (Gillum 1996), but a study of the efficacy of an antidandruff shampoo containing 1% selenium sulfide found no adverse effects after 6 weeks of use by 150 individuals (Neumann et al. 1996).

Application of 100 µL of a lotion (oil-in-water emulsion) containing 0.02% selenium as selenomethionine three times a week to the shaved backs of mice for 39 weeks did not result in significant dermal effects (Burk et al. 1992b). Dermal effects were also not observed in hairless mice treated in the same manner for 49 weeks.

In mice, topical application of selenium sulfide resulted in erythema and skin irritation at 29 mg/kg, acanthosis at 143 mg/kg, and severe skin damage at 714 mg/kg (NTP 1980a).

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to selenium or selenium compounds. However, older reports on eye contact with selenium or selenium compounds indicate that acute exposure to selenium dioxide caused ocular and conjunctival irritation, and caused severe pain, lacrimation, blurred vision, and dulled corneas upon contact (Middleton 1947). Brief exposure to clouds of selenium fumes resulted in lacrimation, irritation, and redness of the eyes (Clinton 1947).

No studies were located regarding ocular effects in laboratory animals after dermal exposure to selenium or selenium compounds.

3.2.3.3 Immunological and Lymphoreticular Effects

A 1988 case report describes a female laboratory technician who developed severely pruritic vesicles between the fingers after 6 months of exposure to a medium containing selenium. After 2 years, the severity of the symptoms increased to include eczema on the face and neck, watering eyes, and two asthma attacks within a 2-month period. Sodium selenite or the medium containing selenium were the only positive patch tests (Senff et al. 1988).

No studies were located regarding immunological and lymphoreticular effects in laboratory animals after dermal exposure to selenium or selenium compounds.

No studies were located regarding the following health effects in humans or laboratory animals after dermal exposure to selenium or to selenium compounds:

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

No studies were located regarding carcinogenic effects in humans after dermal exposure to selenium or selenium compounds.

The results of most animal studies have not indicated that elemental selenium or selenium compounds are carcinogenic when topically applied to the skin of experimental animals (NTP 1980a, 1980b; Shamberger 1970). Several studies indicate that selenium compounds may protect against effects of known dermal carcinogens (polynuclear aromatic hydrocarbons [PAHs] and ultraviolet light). Shamberger (1970) reported that topical application of a solution containing 0.0005% sodium selenide significantly reduced the number of dermal papillomas induced by painting DMBA on the shaved backs of mice. More recently, Burke et al. (1992b) reported orally and topically administered L-selenomethionine decreased ultraviolet burns and skin cancer in albino (BALB:c) and hairless pigmented (Skh:2) female mice.

Only one study was found in which tumor development was reported after topical administration of selenium ointment (Tsuzuki et al. 1960). An unspecified number of mice were exposed to an unspecified amount of ointment containing 2.5, 5.0, 7.5, or 10% elemental selenium 6 days a week for an unspecified period of time by topical administration to hip skin. Tumors developed on the base of the necks of two female mice. Ingestion of the compound was possible because the animals may have licked the ointment. No other details were reported. The study is inconclusive because of the lack of controls, short duration, and inadequate description of the study protocol and results.

The National Toxicology Program (NTP 1980a) conducted a dermal application study of selenium monosulfide. The compound was applied to the skin of groups of 50 male and 50 female Swiss mice at 0, 0.5, or 1.0 mg selenium sulfide/mouse 3 days/week for 86 weeks. The application sites were not covered; therefore, ingestion of the test compounds was possible. The incidence of tumors in the treated groups did not differ significantly from that in the control group.

The NTP (1980b) also tested Selsun, a prescription dandruff shampoo containing 2.5% selenium sulfide (also a mixture of the mono- and disulfides), for carcinogenic properties. Groups of 50 male and

50 female Swiss mice were dermally exposed to a 0, 25, or 50% solution of Selsun in distilled water 3 days/week for 86 weeks. These doses were equivalent to 0, 0.31, or 0.625 mg selenium sulfide/mouse/day. The incidences of alveolar or bronchiolar adenomas or carcinomas in male mice were significantly increased over vehicle control values, but not over untreated control values. There was no significant effect in female mice. Some ingestion of the compound was possible, because the application sites were not covered. Also, the male mice may have been susceptible to another ingredient in the shampoo (the chemical composition of the shampoo was not reported), or the bioassay may have been too short due to decreased survival to detect a carcinogenic effect in females. Male mice that received dermal application of slightly larger doses of selenium sulfide (NTP 1980a) did not develop significantly more cancers than the controls.

3.2.4 Other Routes of Exposure

Endocrine Effects. Intraperitoneal injection of diabetic rats with sodium selenate has been reported to have insulin-like effects, producing a decrease in plasma glucose concentrations (McNeill et al. 1991). However, it is not clear that this is due to an effect of selenium on insulin metabolism, since food and water consumption were also decreased, and this is likely to have produced the decreased glucose levels.

Neurological Effects. Intraperitoneal injection of selenium (3.0 mg Se/kg as sodium selenite) into male Sprague-Dawley rats produced a significant increase (70%) in dopamine overflow from the striatum (as measured by an implanted dialysis probe) with a concomitant significant reduction in HVA levels (Rasekh et al. 1997). DOPAC levels were not changed. Direct infusion of 10 mM selenium into the striatum also produced a significant increase in dopamine overflow accompanied by slight, but significant decrease in HVA and DOPAC. Direct infusion of 10 mM selenium into the nucleus accumbens also produced a rapid and significant increase in dopamine overflow, but with no changes in DOPAC or HVA concentrations. The selenium induced changes in dopamine overflow were suppressed by the dopamine receptor agonist quinpirole.

3.3 GENOTOXICITY

Inorganic selenium compounds have been observed to have both genotoxic and antigenotoxic effects. The antigenotoxic effects generally occur at lower selenium exposure levels than the frank genotoxicity. This discussion will focus on genotoxic effects only. *In vitro* studies of the genotoxicity of selenium

compounds are summarized in Table 3-4, and *in vivo* studies of the genotoxicity of selenium compounds are summarized in Table 3-5.

Selenium dioxide was found to be mutagenic in both the Ames and the VITO-TOX *Salmonella typhimurium* tests of genotoxicity (van der Lelie et al. 1997).

In general, sodium selenite and sodium selenate have produced mixed results in bacterial mutagenicity test systems (Table 3-4). Sodium selenite induced base-pair substitution mutations using *S. typhimurium* and was also positive in the transformation assay using *Bacillus subtilis* (Kramer and Ames 1988; Nakamuro et al. 1976; Noda et al. 1979). However, negative results have also been reported for sodium selenite both in *S. typhimurium* and the rec assay using *B. subtilis* (Lofroth and Ames 1978; Noda et al. 1979). Sodium selenate, on the other hand, has tested positive in *S. typhimurium* (base-pair substitution) and in the rec assay using *B. subtilis* (Lofroth and Ames 1978; Noda et al. 1979), but has tested negative using the transformation assay in *B. subtilis* (Nakamuro et al. 1976).

Results with mammalian cell systems are also mixed, although sodium selenite is more consistently genotoxic in these systems. Sodium selenite has been observed to induce unscheduled deoxyribonucleic acid (DNA) synthesis (UDS), chromosomal aberrations, and sister chromatid exchange in cultured human fibroblasts (Lo et al. 1978; Ray et al. 1978; Whiting et al. 1980); UDS in Chinese hamster V79 cells (Sirianni and Huang 1983); and chromosomal aberrations in cultured Chinese hamster ovary cells (Whiting et al. 1980). However, sodium selenate induced chromosomal aberrations in Chinese hamster ovary cells (Whiting et al. 1980) and UDS in Chinese hamster V79 cells (Sirianni and Huang 1983), but did not induce chromosomal aberrations in human leukocytes or cultured human fibroblasts (Lo et al. 1978; Nakamuro et al. 1976). A comparison of cytotoxicity and induction of tetraploidy in Chinese hamster V79 cells induced by sodium selenite or its major excretory product trimethylselenonium found that sodium selenite was about 1,000 times more cytotoxic than trimethylselenonium, but that neither compound produced a significant change in mitotic index (Ueda et al. 1997).

The addition of glutathione to test mixtures enhances the genotoxicity of sodium selenite, sodium selenate, and sodium selenide in bacterial test systems, indicating that production of a reactive species mutagenic for bacteria occurs via a reductive mechanism following concomitant exposure to these compounds (Whiting et al. 1980). This finding is supported by results in mammalian test systems. For example, in cultured human leukocytes, sodium selenite induces chromosome aberrations and sister chromatid exchanges (Nakamuro et al. 1976; Ray and Altenburg 1978; Ray et al. 1978). Sister chromatid

Table 3-4. Genotoxicity of Selenium *In Vitro*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Prokaryotic organisms:	Mutation			
Salmonella typhimurim	(Na_2SeO_3)		–	Lofrothand Ames 1978
	(Na_2SeO_4)	NT	+	
S. typhimurim	(SeO_2)	NT	+	van der Lelie et al. 1997
S. typhimurim TA100	(Na_2SeO_3)	NT	+	Noda et al. 1979
S. typhimurium TA98, TA1537		NT	–	
S. typhimurium TA100	(Na_2SeO_4)	NT	+	
S. typhimurium TA98, TA1537		NT	–	
Bacillus subtilis rec assay	(Na_2SeO_3)	NT	–	Noda et al. 1979
B. subtilis rec assay	(Na_2SeO_4)	NT	+	Kanematsu et al. 1980
	(SeO_2)	NT	+	
B. subtilis transformation	(SeO_2)	NT	+	Nakamuro et al. 1976
	(Na_2SeO_3)	NT	+	
	(Na_2SeO_4)	NT	–	
Eukaryotic organisms:				
Mammalian cells	Chromosomal aberrations			
Chinese hamster ovary	(Na_2SeO_3)	NT	+	Whiting et al. 1980
	(Na_2SeO_4)	NT	+	
Human leukocytes	(SeO_2)	NT	+	Nakamuro et al. 1976
	(Na_2SeO_3)	NT	+	
	(Na_2SeO_4)	NT	–	
Human lymphocytes	(Na_2SeO_4)	NT	+	Biswas 1997
Human lymphocytes	(Na_2SeO_3)	NT	+	Biswas et al. 2000
	(Na_2SeO_4)	NT	+	

Table 3-4. Genotoxicity of Selenium *In Vitro (continued)*

Species (test system)	End point	Result: With activation	Result: Without activation	Reference
Human lymphocytes	(Na_2SeO_3)	NT	+	Khalil 1989
	(Selenomethionine)	NT	+	
Cultured human fibroblasts	(Na_2SeO_3)	+	+	Lo et al. 1978
	(Na_2SeO_4)	–	–	
	Tetraploidy			
Chinese hamster V79 cells	(Na_2SeO_3)	NT	+	Ueda et al. 1997
	(Trimethylselenonium)	NT	+	
	DNA strand breaks			
Mouse mammary carcinoma cells	Na_2SeO_3)	NT	+	Lu et al. 1995b
	(Na_2SeO_4)	NT	+	
	(Methylselenocyanate)	NT	–	
	(Se-methylselenocysteine)	NT	–	
	Unscheduled DNA synthesis			
Cultured human fibroblasts	(Na_2Se)	NT	+	Whiting et al. 1980
	(Na_2SeO_3)	NT	+	
	(Na_2SeO_4)	NT	+	
	Sister chromatid exchange			
Cultured human fibroblasts	(Na_2SeO_3)	NT	+	Ray et al. 1978
Human lymphocytes	(Na_2SeO_3)	NT	+	Khalil 1989
	(Selenomethionine)	NT	+	
	(Selenocystine)	NT	+	Khalil 1994

– = negative result; + = positive result; DNA = deoxyribonucleic acid; NT = not tested; (Na_2Se) = sodium selenide; (Na_2SeO_3) = sodium selenite; (Na_2SeO_4) = sodium selenate; (SeO_2) = selenium dioxide

Table 3-5. Genotoxicity of Selenium *In Vivo*

Species (test system)	End point	Results	Reference
Human lymphocytes (Na_2SeO_3)	Chromosomal aberrations, sister chromatic exchanges	–	Norppa et al. 1980a
Monkey (*Macaca fisciculari*) bone marrow (L-selenomethionine)	Micronuclei	+ (adult toxic dose) – (fetal at maternally toxic doses)	Choy et al. 1989 Choy et al. 1993
Mouse bone marrow (Na_2SeO_3) (Na_2SeO_4)	Chromosome breaks and spindle disturbances	 + +	Biswas et al. 1997
Mouse bone marrow (Na_2SeO_3) (Na_2SeO_4)	Chromosome breaks and spindle disturbances	 + +	Biswas et al. 1999a
Mouse bone marrow (H_2SeO_3) (Na_2SeO_4)	Micronucleus induction	 + +	Itoh and Shimada 1996
Mouse bone marrow (H_2SeO_3)	Micronucleus induction	+	Rusov et al. 1996
Rat bone marrow (Na_2SeO_3)	Chromosomal aberrations	+	Newton and Lilly 1986
Rat bone marrow (SeS)	Chromosomal aberrations	–	Moore et al. 1996b
Rat bone marrow (SeS)	Micronucleus induction	+	Moore et al. 1996b
Rat spleen (SeS)	Chromosomal aberrations	–	Moore et al. 1996b

Table 3-5. Genotoxicity of Selenium *In Vivo (continued)*

Species (test system)	End point	Results	Reference
Rat spleen (SeS)	Micronucleus induction	–	Moore et al. 1996b
Rat lymphocytes (Na_2SeO_3)	Chromosomal aberrations	–	Newton and Lilly 1986

+ = positive result; – = negative result

exchange was not observed at similar sodium selenite concentrations in a human lymphoblastoid cell line; however, exchanges were observed when these same cells were incubated with sodium selenite and red blood cell lysate (Ray and Altenburg 1978). The observation that internal constituents of red blood cells may contribute to the genotoxicity of sodium selenite supports the suggestion that metabolism is involved in the production of an active species following exposure to sodium selenite in these test systems. The active species responsible for the genotoxic effects is not known.

At high concentrations, sodium selenite induces unscheduled DNA synthesis and chromosome aberrations in cultured human fibroblasts (Lo et al. 1978). The addition of a metabolic activator (S9 fraction) or glutathione increased both the number of aberrations and the toxicity of sodium selenite (Whiting et al. 1980) and sodium selenate (Lo et al. 1978; Whiting et al. 1980).

Sodium selenite, sodium selenide, methylselenocyanate, and Se-methylselenocysteine were all found to be cytotoxic to cells of a mouse mammary carcinoma line; however, only sodium selenite and sodium selenide induced DNA strand breaks (Lu et al. 1995b).

Selenomethionine (Khalil 1989) and selenocystine (Khalil 1994) have tested positive for sister chromatid exchanges in cultured human lymphocytes. Selenomethionine, sodium selenite, and sodium selenate tested positive for chromosomal aberrations in cultured human lymphocytes (Biswas 1997; Biswas et al. 2000; Khalil 1989). Sodium selenite was considerably more clastogenic than sodium selenate (Biswas et al. 2000).

The genotoxicity of selenium monosulfide was assessed in an *in vivo*/*in vitro* micronucleus and chromosome aberration assay in rats (Moore et al. 1996b). Male Wistar rats (4/dose) were administered 25, 50, or 100 mg/kg selenium monosulfide in corn oil. Negative control rats received corn oil by gavage and positive controls were injected intraperitoneally with 20 mg/kg cyclophosphamide. Animals were sacrificed 24 hours after treatment and the femur marrow and spleen were removed and cultured. Spleen and marrow cultures were examined 24 or 48 hours after establishment, respectively. No increase in chromosome aberrations or micronucleus formation in cells from treated rats was observed.

Results of *in vivo* genotoxicity tests have been both negative and positive (Table 3-5). Chromosomal aberrations and sister chromatid exchanges in lymphocytes were not increased in nine neuronal ceroid lipofuscinosis patients treated with intramuscular sodium selenite injections or tablets (0.005–0.05 mg selenium/kg/day) for 1–13.5 months, or in five healthy persons given selenite (0.025 mg/kg/day) for

2 weeks (Norppa et al. 1980a). Among the treated patients, there was no distinction between route of exposure.

Compared to untreated controls, a significant increase in the number of micronuclei was observed in bone marrow cells of macaques treated by nasogastric intubation with L-selenomethionine at a dose of 0.24 mg selenium/kg/day for 15 days (Choy et al. 1989). No effect on the number of micronuclei was observed in macaques treated with L-selenomethionine at a dose of 0.12 mg selenium/kg/day for 19 days. A significant increase in the number of micronuclei in bone marrow cells was not observed in the offspring of macaques treated by nasogastric intubation with L-selenomethionine at a dose of 0.12 mg selenium/kg/day on gestation days 20–50 (Choy et al. 1993). The doses of L-selenomethionine used in these studies produced obvious signs of toxicity (loss of body weight, poor appetite, constipation, depression, weakness) in the macaques.

Chromosomal aberrations were not increased in the lymphocytes of rats given two intravenous doses of sodium selenite at 2.3–2.7 mg selenium/kg (Newton and Lilly 1986). Chromosomal aberrations in bone marrow cells were significantly increased in these rats, but the total dose of selenium was near the intravenous LD_{50} for selenite which has been reported as 5.7 mg selenium/kg in rats (Olson 1986).

Bone marrow cells of male mice gavaged with sodium selenate or sodium selenite showed a significant increase in chromosome breaks and spindle disturbances compared with untreated controls (Biswas et al. 1997, 1999a). The number of chromosomal aberrations increased with dose and was slightly greater with sodium selenite than with sodium selenate. A significant increase in micronucleus formation was observed in bone marrow cells of male mice intraperitoneally injected with selenous acid and in female mice intramuscularly injected with sodium selenite, but not in male mice intraperitoneally injected with sodium selenate (Itoh and Shimada 1996; Rusov et al. 1996).

Selenium appears to affect the ability of liver enzymes to activate some chemical mutagens. Studies in animals exposed orally to sodium selenite in the diet at doses between 0.05 and 0.125 mg selenium/kg/day indicate that selenium may inhibit the mutagenic effect of other chemical agents (Gairola and Chow 1982; Schillaci et al. 1982). In these studies, *S. typhimurium* was used to assess the mutagenicity of DMBA, benzo[a]pyrene (BAP), and 2-aminoanthracene (2AA) in the presence of liver microsomal enzymes from rats fed either a basal diet (0.02–0.15 mg selenium/kg diet or 0.001–0.0075 mg selenium/kg/day) or a sodium selenate-supplemented diet (basal diet plus 1–5 mg selenium/kg/diet or 0.05–0.25 mg selenium/kg/day) for 3–20 weeks. DMBA and 2AA were found to be less mutagenic in the

presence of liver microsomal enzymes taken from rats fed the selenium-supplemented diets than in the presence of microsomal enzymes taken from rats fed the basal diet; BAP mutagenicity was not changed.

The genotoxicity of selenium monosulfide was assessed in an *in vivo* micronucleus and chromosome aberration assays in rats (Moore et al. 1996b). Male Wistar rats (5/dose/timepoint) were administered 12.5, 25, or 50 mg/kg selenium monosulfide in corn oil. Negative control rats received corn oil by gavage and positive controls were injected intraperitoneally with 20 mg/kg cyclophosphamide. Animals were sacrificed 24, 36, or 48 hours after treatment and the femur marrow and spleen cells were examined. A small, but significant increase in micronucleated bone marrow cells was observed 24 hours after treatment with 50 mg/kg selenium monosulfide and 48 hours after treatment with 12.5 mg/kg selenium monosulfide. Selenium monosulfide was cytotoxic at the 50 mg/kg dose after 24 hours. No increase in micronucleus formation was observed in the spleen. No increase in chromosome aberrations was observed in the bone marrow or spleen.

3.4 TOXICOKINETICS

Occupational studies indicate that humans absorb elemental selenium dusts and other selenium compounds, but quantitative inhalation toxicokinetic studies in humans have not been done. Studies in dogs and rats indicate that following inhalation exposure, the rate and extent of absorption vary with the chemical form of selenium. Studies in humans and experimental animals indicate that, when ingested, several selenium compounds including selenite, selenate, and selenomethionine are readily absorbed, often to greater than 80% of the administered dose. Although a study of humans did not detect evidence of dermal absorption of selenomethionine, one study of mice indicates selenomethionine can be absorbed dermally. There is little or no information available on the absorption of selenium sulfides, but selenium disulfides are not believed to be absorbed through intact skin.

Selenium accumulates in many organ systems in the body; in general, the highest concentrations are found in the liver and kidney (Table 3-6). Selenium concentrations in tissues do not seem to be correlated with effects. Tissue concentrations were highest in pigs fed D,L-selenomethionine, while a similar dose of selenium (form not stated) given as *A. bisulcatus* was a more potent neurotoxin. Blood, hair, and nails also contain selenium, and selenium has been found in human milk (Table 3-7). In addition, selenium is subject to placental transfer.

Table 3-6. Selenium Concentrations in Human Tissues[a,b]

Selenium concentration				
Mean	SD	Range	Country	Reference
Fetal tissues				
Liver (µg selenium/g)				
2.8	0.2		United States	Robkin et al. 1973[c]
Blood (mg selenium/L)				
0.12	0.008		United States	Hadjimarkos et al. 1959
1.04	0.28		United States	Baglan et al. 1974[c]
0.070	0.017		New Zealand	Thompson and Robinson 1980
0.061	0.014		Scandanavia	Korpela et al. 1984
Erythrocytes (mg selenium/L)				
0.39	0.08		United States	Rudolph and Wong 1978
0.149			Scandanavia	Haga and Lunde 1978
0.104	0.026		New Zealand	Thompson and Robinson 1980
Plasma (mg selenium/L)				
0.13	0.03		United States	Rudolph and Wong 1978
0.033	0.008		New Zealand	Thompson and Robinson 1980
Serum (mg selenium/L)				
0.052			Scandanavia	Haga and Lunde 1978
Adult/Infant tissues				
Adrenal gland (µg selenium/g)				
0.46	0.03		United States	Blotcky et al. 1979
0.21 (infant) 0.36 (adult)			Canada	Dickson and Tomlinson 1967
Brain (µg selenium/g)				
		0.114–0.171	Denmark	Larsen et al. 1979
0.110	0.021		Germany	Oster et al. 1988c
0.16 (infant) 0.27 (adult)			Canada	Dickson and Tomlinson 1967
		0.115–0.222	Japan	Ejima et al. 1996
Fat (µg selenium/g)				
0.09 (infant) 0.12 (adult)			Canada	Dickson and Tomlinson 1967

Table 3-6. Selenium Concentrations in Human Tissues[a,b] (*continued)*

Selenium concentration				
Mean	SD	Range	Country	Reference
Adult/Infant tissues (*cont.*)				
Gonad (µg selenium/g)				
0.46 (infant) 0.47 (adult)			Canada	Dickson and Tomlinson 1967
Heart (µg selenium/g)				
0.33	0.13		United States	Blotcky et al. 1979
0.170	0.032		Germany	Oster et al. 1988c
0.155	0.030 (LV)			
0.55 (infant) 0.22 (adult)			Canada	Dickson and Tomlinson 1967
Intestine (µg selenium/g)				
0.31 (infant) 0.22 (adult)			Canada	Dickson and Tomlinson 1967
Kidney (µg selenium/g)				
0.89	0.11		United State	Blotcky et al. 1979
0.771	0.169		Germany	Oster et al. 1988c
0..92 (infant) 0.63 (adult)			Canada	Dickson and Tomlinson 1967
0.78	0.19	0.36–1.29	Sweden	Muramatsu and Parr 1988
Liver (µg selenium/g)				
0.62	0.04		United States	Blotcky et al. 1979
0.50	0.08	0.35–0.65	United States	Zeisler et al. 1984
1.73	0.24		United States	McConnell et al. 1975[c]
		0.27–0.51	Denmark	Larsen et al. 1979
0.291	0.078		Germany	Oster et al. 1988c
0.995	0.308		Finland	Alfthan et al. 1991[c]
0.45	0.11		Finland	Aaseth et al. 1990
0.06			Bulgaria	Damyanova 1983
0.33	0.12	0.082–0.64	Sweden	Muramatsu and Parr 1988
0.19	0.05	0.10–0.27	New Zealand	Casey et al. 1983
0.34 (infant) 0.39 (adult)			Canada	Dickson and Tomlinson 1967

Table 3-6. Selenium Concentrations in Human Tissues[a,b] (*continued)*

Selenium concentration				
Mean	SD	Range	Country	Reference
Adult/Infant tissues (*cont.*)				
Lung (µg selenium/g)				
0.30	0.02		United States	Blotcky et al. 1979
0.132	0.033		Germany	Oster et al. 1988c
0.17 (infant) 0.21 (adult)			Canada	Dickson and Tomlinson 1967
Pancreas (µg selenium/g)				
0.55	0.13		United States	Blotcky et al. 1979
0.63	0.07		United States	McConnell et al. 1975[c]
0.05 (infant) 0.13 (adult)			Canada	Dickson and Tomlinson 1967
Prostate (µg selenium/g)				
0.26	0.02		United States	Blotcky et al. 1979
0.150	0.035		Germany	Oster et al. 1988c
Skeletal muscle (µg selenium/g)				
0.40	0.20		United States	Blotcky et al. 1979
0.111	0.017		Germany	Oster et al. 1988c
0.31 (infant) 0.40 (adult)			Canada	Dickson and Tomlinson 1967
		0.13–0.21	Denmark	Larsen et al. 1979
Skin (µg selenium/g)				
0.24	0.02		United States	Blotcky et al. 1979
Spleen (µg selenium/g)				
0.37	0.03		United States	Blotcky et al. 1979
0.226	0.044		Germany	Oster et al. 1988c
0.37 (infant) 0.27 (adult)			Canada	Dickson and Tomlinson 1967
Stomach (µg selenium/g)				
0.19 (infant) 0.17 (adult)			Canada	Dickson and Tomlinson 1967

Table 3-6. Selenium Concentrations in Human Tissues[a,b] (*continued)*

Selenium concentration				
Mean	SD	Range	Country	Reference
Adult/Infant tissues (*cont.*)				
Testis (µg selenium/g)				
0.28	0.03		United States	Blotcky et al. 1979
0.274	0.048		Germany	Oster et al. 1988c
Thyroid (µg selenium/g)				
1.02	0.20		United States	Blotcky et al. 1979
0.72	0.44	0.15–1.90	Finland	Aaseth et al. 1990
0.64 (infant) 1.24 (adult)			Canada	Dickson and Tomlinson 1967

[a]General population measures unless otherwise noted
[b]Selenium concentrations in adult blood and blood components, urine, hair, nails, milk, placenta, and semen are found in Table 3-7
[c]Dry weight

LV = left ventricle; RV = right ventricle; SD = standard deviation

Table 3-7. Biomarkers: Selenium Concentrations in Human Tissues and Fluids[a]

Selenium concentration				
Mean	SD	Range	Country	Reference
Whole blood (mg selenium/L)				
0.132	0.029	0.08–0.13	United States	Corden et al. 1989
0.206		0.10–0.30	United States	Allaway et al. 1968
0.109	0.015		United States	Dworkin et al. 1986
0.157		0.103–0.191	United States	Shamberger 1983
0.182	0.037		Canada	Dickson and Tomlinson 1967
0.095	0.009		China	Zhu 1981
0.095	0.091		China	Yang et al. 1983
0.164	0.032		Greece	Bratakos et al. 1990
0.108	0.006	0.076–0.140	Italy	Minoia et al. 1990
		0.079–0.103	Finland	Jaakkola et al. 1983
		0.080–0.089	Finland	Kumpusalo et al. 1990[b]
		0.077–0.089	Finland	Kumpusalo et al. 1990[c]
0.069	0.018		New Zealand	Thomson and Robinson 1980[d]
0.059	0.012		New Zealand	Rea et al. 1979
0.092	0.001	0.06–0.013	Germany	Oster et al. 1988b
Erythrocyte (mg selenium/L)				
0.174		0.11–0.28	United States	Meyer and Verreault 1987
0.13	0.02		United States	Dworkin et al. 1986
0.52	0.05		United States	Rudolph and Wong 1978[d]
0.131	0.002	0.060–0.210	Germany	Oster et al. 1988b
		0.057–0.087	New Zealand	Watkinson 1981
0.074	0.016		New Zealand	Rea et al. 1979
0.103	0.030		New Zealand	Thomson and Robinson 1980
Plasma (mg selenium/L)				
0.155		0.081–0.225	United States	Clark et al. 1984
0.095	0.016		United States	Dworkin et al. 1986
0.21	0.03		United States	Rudolph and Wong 1978[d]
0.148			United States	Coates et al. 1988
0.081	0.016		Canada	Dickson and Tomlinson 1967
0.153	0.021		Japan	Hojo 1987
0.089	0.014		Netherlands	van't Veer et al. 1990
0.081	0.001	0.056–0.105	Italy	Minoia et al. 1990
0.118	0.027	0.064–0.173	Italy	Sesana et al. 1992
0.048	0.010		New Zealand	Rea et al. 1979
0.041	0.011		New Zealand	Thomson and Robinson 1980[d]

Table 3-7. Biomarkers: Selenium Concentrations in Human Tissues and Fluids (*continued*)

Selenium concentration				
Mean	SD	Range	Country	Reference
Serum (mg selenium/L)				
0.136	0.002		United States	Willett et al. 1983
0.110	0.016		United States	Menkes et al. 1986
0.162	1.48		United States	Coates et al. 1988
0.07			United States	McConnell et al. 1975[e]
0.198	0.055	0.123–0.363	United States	Longnecker et al. 1991
0.143	0.016		Canada	Lalonde et al. 1982[f]
0.081	0.001	0.033–0.121	Italy	Minoia et al. 1990
		0.087–0.093	Italy	Morisi et al. 1989
0.118	0.016	0.087–0.308	Finland	Luoma et al. 1992
0.055	0.001		Finland	Virtamo et al. 1987
0.073	0.015		South Africa	Heese et al. 1988[d]
0.207		0.07–0.81	Venezuela	Brätter et al. 1991a
		0.229–0.621	Venezuela	Brätter and Negretti De Brätter 1996
Urine (mg selenium/L)				
0.034	0.024		England	Glover 1970
0.058	0.026	0.020–0.113	Japan	Hojo 1981a
0.026	0.012		China	Yang et al. 1983
0.024	0.002		Greece	Bratakos et al. 1990
0.022	0.002	0.002–0.031	Italy	Minoia et al. 1990
Hair (µg selenium/g)				
0.64	0.02		United States	Thimaya and Ganapathy 1982
0.359	0.004		China	Zhu 1981
0.36	0.17		China	Yang et al. 1983
0.42	0.88		Greece	Bratakos et al. 1990
0.42	0.10	0.21–0.63	Sweden	Muramatsu and Parr 1988[e]
3.40	2.0	0.95–9.6 (female)	Japan	Imahori et al. 1979[e]
3.70	2.3	0.06–14.2 (male)		
1.02	1.04	maternal	England	Razagui and Haswell 1997
0.63	0.52	neonatal		
0.54	0.34	maternal	Spain	Bermejo Barrera et al. 2000
0.77	0.24	child		

Table 3-7. Biomarkers: Selenium Concentrations in Human Tissues and Fluids (*continued*)

Selenium concentration				
Mean	SD	Range	Country	Reference
Nails (µg selenium/g)				
1.56	0.58	0.083–3.82	United States	Longnecker et al. 1991
0.82	0.174		United States	Hunter et al. 1990a
0.63	0.12		Netherlands	van't Veer et al. 1990
0.54	0.91		Greece	Bratakos et al. 1990
0.78		0.085–2.75	Netherlands	Van Noord et al. 1992
Milk (µg selenium/mL)				
		0.208–0.256	Africa	Funk et al. 1990[b]
0.018	0.004	0.007–0.033	United States	Shrearer and Hadjimarkos 1975
0.021		0.013–0.053	United States	Hadjimarkos 1963
0.016	0.005			Smith et al. 1990
0.026			United States	Ellis et al. 1990
0.062	0.055	0.015–0.214	Chile	Cortez 1984
0.010	0.002	0.006–0.013	Finland	Kumpulainen 1983
0.011			Austria	Li et al. 1999
0.012			Germany	Michalke and Schramel 1998
		0.025–0.250	Venezuela	Brätter et al. 1991a
		0.043–0.112	Venezuela	Brätter and Negretti De Brätter 1996
Placenta (mg selenium/L)				
1.70	0.61		United States	Baglan et al. 1974[e]
0.193	0.016		United States	Korpela et al. 1984
0.18	0.007		United States	Hadjimarkos et al. 1959
Semen (µg selenium/g)				
0.063	0.020	0.016–0.131	Singapore	Roy et al. 1990
1.80	0.11		Finland	Suistomaa et al. 1987[e]

[a]General population measures unless otherwise noted
[b]Range of mean concentration
[c]Range of mean concentrations for multivitamin users
[d]Only women were sampled
[e]Dry weight
[f]Only men were sampled

SD = standard deviation

As a component of glutathione peroxidase and the iodothyronine 5'-deiodinases, selenium is an essential micronutrient for humans. Its role in the deiodinase enzymes may be one reason that children require more selenium for growth than adults. Selenium is also a component of the enzyme thioredoxin reductase, which catalyses the NADPH-dependent reduction of the redox protein thioredoxin. Other selenium-containing proteins of unknown functions, including selenoprotein P found in the plasma, have also been identified. Excess selenium administered as selenite and selenate has been shown to be metabolized to methylated compounds and excreted.

Selenium is primarily eliminated in the urine and feces in both humans and laboratory animals. The distribution of selenium between the two routes seems to vary with the level of exposure and time after exposure. The form of selenium excreted is dependent on the form of selenium that was ingested. In cases of acute exposure to toxic concentrations of selenium or selenium compounds, significant amounts of selenium can be eliminated in the breath, causing the characteristic "garlic breath."

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Studies regarding the absorption of selenium in humans following inhalation exposure are limited to occupational studies. Glover (1970) examined urinary selenium levels of workers employed in a selenium rectifier plant. Workers exposed to higher levels of unspecified inorganic selenium compounds in the air excreted higher levels of selenium in their urine than workers in other areas of the plant with lower concentrations of selenium in the air. Although the study indicates that selenium was absorbed from the lungs of the workers, the nonspecific exposure levels and lack of compound identification precluded an estimate of the extent and rate of absorption from the lungs. Significantly increased serum selenium levels were reported for workers at a rubber tire repair shop in Toluca City, Mexico compared with a group of unexposed individuals from the same city (Sánchez-Ocampo et al. 1996). The workers in this study were exposed to selenium (no levels reported) from vulcanized rubber, both as dust in the air and from handling the tires; thus, it is not possible to attribute absorption to a single route.

Studies using dogs and rats indicate that absorption of selenium following inhalation exposure is extensive, although the rate of absorption depends on the chemical form of selenium. In rats (Medinsky et al. 1981a) and dogs (Weissman et al. 1983), the absorption of selenium following inhalation exposure to selenious acid aerosol is approximately twice as rapid as the absorption of selenium following

inhalation exposure to elemental selenium aerosol. However, Medinsky et al. (1981a) found that with either form after 4 days most of the selenium was absorbed following inhalation exposure and that the distribution of selenium in the body tissues was identical, suggesting that selenium entered the same body pool following pulmonary uptake (Medinsky et al. 1981a).

3.4.1.2 Oral Exposure

Selenium compounds are readily absorbed from the human gastrointestinal tract. The bioavailability of ingested selenium can be affected by the physical state of the compound (e.g., solid or solution), the chemical form of selenium (e.g., organic, inorganic), and the dosing regimen. However, in general, it appears that the degree of selenium absorption (i.e., percent of administered dose absorbed) in humans is independent of the exposure level, but that in some cases, absorption is greater when selenium deficiency exists.

In humans, absorption of sodium selenite or selenomethionine can exceed 80% for both small and relatively large doses (Griffiths et al. 1976; Thomson 1974; Thomson and Stewart 1974; Thomson et al. 1977). A total of 90–95% of a small amount of sodium selenite (0.010 mg selenium/person) administered in aqueous solution was absorbed (Thomson 1974). Absorption of a large dose (1.0 mg/person) of either sodium selenite or selenomethionine was 90–95 and 97% of the administered dose, respectively (Thomson et al. 1977). These data indicate a lack of homeostatic control over the dose range tested. However, Martin et al. (1989a) reported increased absorption of selenium from sodium selenite in an aqueous solution by healthy male volunteers kept on a selenium-deficient diet, indicating that a lower-bound homeostatic control on absorption exists. Griffiths et al. (1976) reported 96–97% absorption of a single dose of 0.002 mg selenium administered as selenomethionine in solution. Similarly, Thomson et al. (1977) reported 97% absorption of a single large dose of 1.0 mg selenium administered as selenomethionine in solution to one subject. The subjects in these studies were New Zealand women.

Other studies have indicated that humans might absorb selenomethionine more efficiently than sodium selenite (Moser-Veillon et al. 1992; Swanson et al. 1991). Young et al. (1982) studied human absorption of dietary selenium in young men in the United States. The men ate either ^{75}Se-labeled chicken alone (0.013 mg selenium/person) or the chicken plus supplemental labeled sodium selenite (0.071 mg selenium/person in a solution mixed with the meal). Eighty percent of the selenium in the chicken meat was absorbed, but less than 30% of the selenium administered as sodium selenite was absorbed. Similarly, Robinson et al. (1978) found that 75% of selenomethionine, but only 46% of selenite, was

absorbed during a 10–11-week administration of solutions providing 0.0013–0.0023 mg selenium/kg/day to New Zealand women. It is not clear why the estimated absorption of sodium selenite varied between 46 and 30% in these trials.

Experimental animals also efficiently absorb selenium compounds from the gut independent of the level of selenium exposure. Several studies have reported absorption of 80–100% in rats given dietary selenium administered as sodium selenite, sodium selenate, selenomethionine, or selenocystine (Furchner et al. 1975; Thomson and Stewart 1973). Other animal species also readily absorb orally administered selenium compounds. Furchner et al. (1975) estimated that over 90% of an oral dose of selenious acid was absorbed in mice and dogs, although monkeys absorbed less of the administered dose (amount unspecified). Using an *in vivo* perfusion method in which selenite was added directly to the duodenal end of the small intestine, the absorption of selenite was found to be linear (slope=0.0386) over the concentration range of 1–200 µM (Chen et al. 1993).

In one study of rats, absorption of selenite or selenomethionine into the blood stream following oral exposure occurred primarily in the duodenum and, to a lesser extent, in the jejunum and the ileum (Whanger et al. 1976). Compared to the small intestine, little selenium was absorbed from the stomach (Whanger et al. 1976), and it was not determined whether absorption occurred in the large intestine. In an *in vitro* study using everted intestinal sacs from hamsters, Spencer and Blau (1962) found that selenomethionine was transported against a concentration gradient with the same characteristics as methionine. Selenomethionine was not found to be degraded during transport. This study suggests that in the intestines, methionine and selenomethionine share the same transport mechanism.

A comparison of absorption of selenium by selenium-depleted rats after oral administration of sodium selenate, selenomethionine, or methyl selenocysteine (from high-selenium broccoli) found that gross absorption of selenium from methyl selenocysteine was significantly lower (85%) than from sodium selenate or selenomethionine (91%), further, true selenium absorption adjusted for urinary excretion was significantly different for methyl selenocysteine, sodium selenate, and selenomethionine, with the lowest absorption for methyl selenocysteine and the highest for selenomethionine (Finley 1998). Absorption of selenium from selenomethionine was not significantly lower than from sodium selenate.

In vivo experiments with ligated rat intestines have shown that there is significantly higher absorption and transfer to the body of selenium as selenocystine or selenodiglutathione than selenium as selenite from ligated loops of ileum, but that absorption of the three forms of selenium in the jejunum was

approximately similar (Vendeland et al. 1992). *In vitro* experiments with brush border membrane vesicles derived from rat intestines have shown dramatic differences in the uptake and binding of selenium depending on the form in which it is presented, with absorption of organic forms being much more efficient than absorption from selenite or selenate (Vendeland et al. 1992, 1994). Selenium from selenocystine or selenodiglutathione was absorbed 10 times more quickly than selenium from sodium selenite (Vendeland et al. 1992). Similarly, selenium was much more efficiently absorbed from selenomethionine than from selenite or selenate (Vendeland et al. 1994). Binding also varied between selenomethionine, selenite, and selenate, with selenite binding exceeding that of selenate by 37-fold and selenomethionine exceeding selenite by 14-fold (Vendeland et al. 1994).

3.4.1.3 Dermal Exposure

Dermal absorption was tested in eight women at a maximum dose of 0.0029 mg selenium/kg as selenomethionine (0.05% L-selenomethionine in a lotion). No detectable increase in serum selenium concentrations was observed; but because the concentrations tested were so low, absorption cannot be ruled out (Burke et al. 1992a). Absorption of selenium disulfide was examined using a monthly 24-hour urine specimen in 16 persons who washed their hair weekly with a 1% selenium disulfide shampoo. No differences were found from control urinary selenium levels over the 1-year exposure period (Cummins and Kimura 1971). No absorption of selenium from selenium sulfide was seen in 15 persons who applied a 2.5% selenium sulfide suspension to their torsos and allowed it to remain on the body overnight (Kalivas 1993).

Mice were treated with a maximum of 0.02% selenium as selenomethionine by topical application of a lotion three times per week for 39 weeks to the shaved back and ears (size of area not specified). The applied dose was 0.29 mg/kg/day. Controls received the lotion without selenium. Dermal effects were not observed in the selenomethionine-treated mice. However, treated animals had significantly higher concentrations of selenium than the controls in the liver and ventral skin away from the application site (Burke et al. 1992b). These data suggest that mice can absorb topically applied selenomethionine, but since the areas were not occluded, some oral absorption during grooming is also possible.

3.4.1.4 Other Routes of Exposure

3.4.2 Distribution

Most studies report similar distribution patterns for both organic and inorganic selenium compounds tested. Normal levels of selenium found in various human tissues are shown in Table 3-6. Selenium concentrations in human fluids and tissues that are easily collected (e.g., placenta) are provided in Section 3.8.2, Biomarkers Used to Identify or Quantify Exposure to Selenium. Selenium from sodium selenite and sodium selenate is found at the highest concentrations in the liver and kidney of humans and other animals following oral administration or intravenous or subcutaneous injection (Cavalieri et al. 1966; Heinrich and Kelsey 1955; Jereb et al. 1975; Thomson and Stewart 1973). Similarly, monkeys receiving high doses of L-selenomethionine orally for up to 30 days accumulated the highest concentrations of selenium in the liver and kidneys (Willhite et al. 1992). Selenium from selenomethionine tends to be retained in tissues at higher concentrations (3–10-fold greater) and for longer periods of time than inorganic selenium compounds. The increased selenium tissue concentrations are not due to the slightly greater absorbance of selenomethionine (Butler et al. 1990; Gronbaek and Thorlacius-Ussing 1992; Ip and Hayes 1989; Salbe and Levander 1990b), but rather to the slower elimination as a consequence of its incorporation into body proteins (Stadtman 1983, 1987, 1990).

3.4.2.1 Inhalation Exposure

No studies were located regarding the distribution of selenium in humans after inhalation of elemental selenium or selenium compounds.

Weissman et al. (1983) reported that selenium concentrated in the liver, kidney, spleen, and lungs of dogs following inhalation exposure to selenious acid or elemental selenium aerosols.

3.4.2.2 Oral Exposure

A study of 100 paired samples of maternal and neonate hair found that the concentration in neonatal hair (0.63±0.52 µg/g) was lower than in maternal hair (1.02±1.04 µg/g), but the results were not analyzed statistically (Razagui and Haswell 1997). Levels of selenium in 30 paired samples of the hair of a mother and her child found no correlation between the selenium concentration of the hair of the mother and her child (Bermejo Barrera et al. 2000). The average level of selenium in the children's hair (0.77±0.24 µg/g)

was higher than that of their mothers (0.54±0.34 μg/g). The higher concentration of selenium in the children's hair could represent increased absorption or retention, but no information was provided in the study as to the age of the children or to possible differences in dietary intake of selenium between mother and child.

In rats and dogs, the selenium arising from sodium selenite administered in drinking water or in the diet is widely distributed in the body, although concentrated primarily in the liver and kidney (Furchner et al. 1975; Sohn et al. 1991; Thomson and Stewart 1973).

In most studies, selenium from selenomethionine accumulates in tissues to a greater extent than equal administered doses of selenium from selenite or selenate. Behne et al. (1991) reported higher liver and muscle selenium concentrations in rats receiving selenium orally as selenomethionine for 3 or 6 weeks than as selenite for the same length of time. Ip and Hayes (1989) reported similar results for blood, liver, kidney, and skeletal muscle. Salbe and Levander (1990b) compared distribution of dietary selenomethionine and selenate in rats and found higher selenium concentrations in plasma, erythrocytes, liver, muscle, hair, and nails in animals receiving selenomethionine. (Hair and nails have been used to gauge long-term human selenium exposure and were, therefore, included in this study.) Monkeys receiving selenomethionine in drinking water for 11 months had selenium concentrations in plasma, erythrocytes, liver, muscle, and hair that were 3–10-fold greater than monkeys receiving selenite (Butler et al. 1990). The higher levels of selenium found after selenomethionine compared to selenite treatment are likely a result of a greater retention of selenium from selenomethionine, rather than a difference in absorption. Butler et al. (1990) indicate that dietary ascorbic acid can reduce selenite absorption, but not selenomethionine absorption. Therefore, the differential effect of ascorbic acid on selenium absorption may have contributed to the difference in selenium content of tissues observed in monkeys treated with selenite, compared to monkeys treated with selenomethionine. Two studies of rats indicate that the central nervous system also concentrates more selenium when administered as selenomethionine than when administered as inorganic selenium compounds (Gronbaek and Thorlacius-Ussing 1992; Zi-Jian Jie 1992).

A comparison of distribution of selenium in selenium-depleted rats after oral administration of sodium selenite, sodium selenate, selenomethionine, or methyl selenocysteine (from high-selenium broccoli) revealed that the rate of restoration of selenium in the liver and muscle was significantly slower for methyl selenocysteine than other forms of selenium (Finley 1998). The rate of repletion in muscle was significantly faster for selenomethionine than other groups, but kidney and plasma showed no significant

difference in the rate of repletion for any form of selenium. The rate of repletion of glutathione peroxidase activity in the tissues was similar to the rate of repletion of the tissue itself and was slowest when methyl selenium was the administered form.

Another study of distribution of selenium in selenium-deficient rats fed either sodium selenite or selenomethionine found that concentration of selenium in blood and hair increased with administered dose, but was higher for selenium administered as selenomethionine (Shiobara et al. 1998).

A study of dietary supplementation of female pigs with 0.1 or 0.3 ppm selenium from a selenium-enriched yeast or from sodium selenite (doses not given) from 60 days before breeding until weaning found that the concentration of selenium in milk, dam, and offspring tissues increased with the dose of selenium administered and was higher when the source of selenium was the selenium-enriched yeast (Mahan and Kim 1996).

A study using pigs indicates that tissue levels of selenium do not correlate with effects. Tissue concentrations of selenium were higher in pigs fed 1.25 mg selenium/kg/day as D,L-selenomethionine than in pigs fed the same dose of selenium as *A. bisulcatus* or selenate, although neurological effects were more severe and occurred after fewer days of treatment with *A. bisulcatus* (Panter et al. 1996). The form of selenium in *A. bisulcatus* is unknown, although Panter et al. (1996) indicate that it is nonprotein.

In poultry, selenium is concentrated in the pancreas to a greater extent following oral administration of selenomethionine than following oral administration of sodium selenite (Cantor et al. 1975). The differential ability of the two compounds to concentrate in the pancreas of birds may explain why selenium administered as selenomethionine is more effective than the same dose of selenium administered as sodium selenite in preventing pancreatic fibrosis in chicks, a condition indicative of selenium deficiency (Cantor et al. 1975).

The distribution profiles of single oral or intravenous doses of selenium (2 mg selenium/kg as sodium selenite) administered to Wistar rats were dependent on the route of administration (Kaneko et al. 1999). Selenium concentration was highest in the kidney or liver, followed by the heart, lung, or spleen; then plasma and the brain. Oral administration produced lower doses of selenium than injection in all organs except the kidney where levels produced by the two routes were comparable (this may reflect the importance of urine as a route of excretion).

Following oral exposure, selenium is found in human milk (Brätter and Negretti De Brätter 1996; Brätter et al. 1991b; Li et al. 1999; Michalke and Schramel 1998; Moser-Veillon et al. 1992; Rodríguez Rodríguez et al. 1999; Viitak et al. 1995; Yang 1989b). Selenium is also found in the milk of mice, rats, dogs, pigs, cows, and monkeys (Abdelrahman and Kincaid 1995; Archimbaud et al. 1992; Banuelos and Mayland 2000; Chhabra and Rao 1994; Hawkes et al. 1994; Mahan and Kim 1996; Parizek et al. 1971a). This supplies offspring with selenium during the time period in which they are fed exclusively on milk (about 6 months for humans). Transplacental transfer of selenium has been demonstrated in humans, rats, hamsters, dogs, pigs, and monkeys (Archimbaud et al. 1992; Choy et al. 1993; Hawkes et al. 1994; Jandial et al. 1976; Mahan and Kim 1996; Parizek et al. 1971a; Willhite et al. 1990).

3.4.2.3 Dermal Exposure

Although unable to detect increased selenium in human females exposed to selenomethionine dermally, Burke and coworkers found elevated liver and skin selenium concentrations in mice treated with a topical lotion containing selenomethionine applied to the shaved back and ears (size of area not specified), although since the areas were not occluded, some oral absorption during grooming is also possible (Burke et al. 1992a, 1992b). In rats, between 9 and 27% of dermally applied selenious acid was absorbed, as measured in ^{75}Se radioisotope studies (Medinsky et al. 1981b).

3.4.2.4 Other Routes of Exposure

In humans, selenium has been found to be widely distributed to organs and tissues following injection of sodium selenite, sodium selenate, and selenomethionine, with the highest concentrations generally found in the liver and kidneys (Ben-Porath and Kaplan 1969; Cavalieri et al. 1966; Jereb et al. 1975; Lathrop et al. 1972). In studies involving injection of radiolabelled selenium, the pancreas accumulated high concentrations of radiolabelled selenium immediately following injection; but within hours the selenium rapidly disappeared from this organ (Lathrop et al. 1972). Using an *in vitro*, dually perfused, human term placenta, selenite has also been shown to cross the human placenta (Eisenmann and Miller 1994). Further, following intravenous injection, ^{75}Se from selenomethionine was found to cross the near-term human placenta (Jandial et al. 1976).

There is a rapid decline in serum selenium levels 1 hour after intravenous administration of sodium selenite or sodium selenate to humans (Burk 1974; Nelp and Blumberg 1965). Burk (1974) found that 50% of the plasma selenium was protein-bound within the first 2 hours after administration; 85% was

bound within 4–6 hours after administration; and 95% was bound after 24 hours. Circulating alpha-2 globulins have been reported to have the greatest affinity for selenium (Hirooka and Galambos 1966a). Burk (1974) found that lipoproteins, primarily the very low density lipoprotein (VLDL) and the low-density lipoprotein (LDL) fractions, were also involved in selenium binding.

In vitro studies of human plasma and whole blood incubated with sodium selenite have indicated that selenite is accumulated in erythrocytes by an active transport mechanism (Lee et al. 1969). Several studies indicate that the selenite is chemically altered in the erythrocyte and then transported back into the plasma, where the selenium metabolite binds to plasma proteins (Burk 1974; Hirooka and Galambos 1966a; Lee et al. 1969).

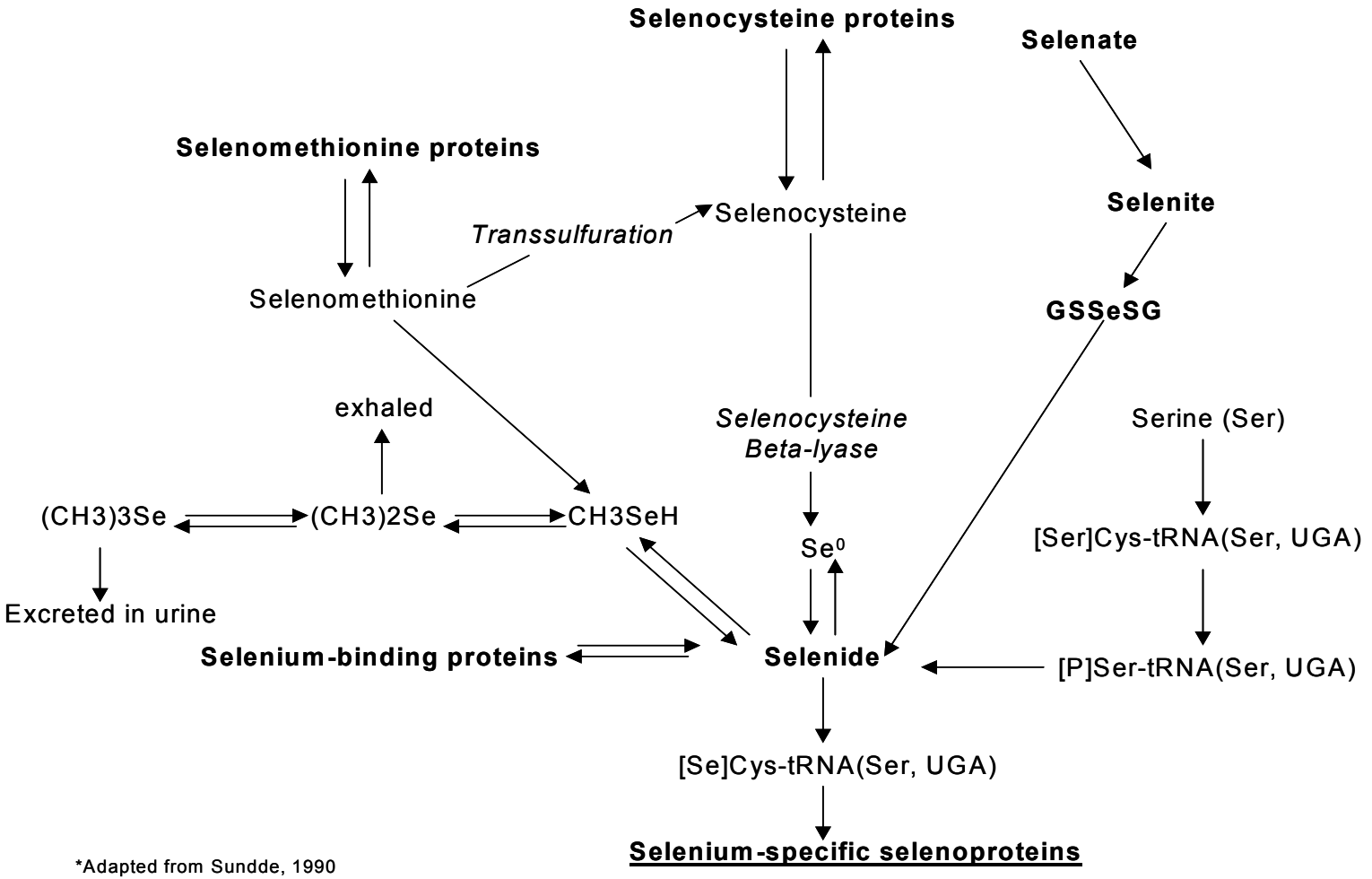
A high degree of protein binding of selenium in the plasma has also been demonstrated in experimental animals. Sandholm (1973) found that selenite administered intravenously to mice can be metabolically altered by erythrocytes to a form that binds to plasma proteins. In mice, rats, and dogs, selenite initially binds to albumin. Later, selenite can be found bound to alpha and gamma globulins in rats and to alpha-2 and beta-1 globulins in dogs (Imbach and Sternberg 1967; Sternberg and Imbach 1967).

3.4.3 Metabolism

Selenium is an essential element, and the metabolism of selenium resulting in incorporation into selenoproteins is outlined in Figure 3-4. Sunde (1990) has defined four classes of selenoproteins: selenium-specific proteins, proteins incorporating selenocystiene at cysteine codons, proteins incorporating selenomethionine at methionine position in those proteins, and proteins that bind selenide nonspecifically. The selenium-specific proteins, which include the enzymes glutathione peroxidase, thyoxine reductase, and iodothyronine 5'-deiodinase, constitute the most physiologically important class of selenoproteins. These proteins contain selenocysteine that is incorporated cotranslationally using selenide and serine as the precursors. This process is specified by a uracil-guanine-adenine (UGA) codon, which usually functions as a stop codon. A stem-loop structure in the 3' untranslated region is required for UGA to specify selenocysteine (Berry et al. 1991). This cotranslational process is the only known pathway for the production of selenocysteine in humans. In contrast to selenocysteine, selenomethionine cannot be biosynthesized by human tissues (Levander 1986).

The second and third classes of selenoproteins form in a similar manner: selenomethionine bound to the transfer ribonucleic acid (tRNA) for methionine competes with methionine bound to the tRNA for

Figure 3-4. Metabolic Pathways for Selenium*



*Adapted from Sundde, 1990

methionine at methionine codons, and selenocysteine bound to the tRNA for cysteine competes with cysteine bound to the tRNA for cysteine at cysteine codons (Sunde 1990). The amount of selenoamino acids incorporated into protein is dependent on the ratio of the selenoamino acid and the amino acid bound to the amino acid tRNA.

The last class of selenoproteins contains the selenium binding proteins. This is an operational class defined by Sunde (1990) as "selenoproteins with selenium bound tightly enough so that the selenium remains attached during standard protein purification procedures that produce discrete selenium labeled species." This class contains selenoproteins that have not been fully characterized.

As indicated in Figure 3-4, selenide, which can nonspecifically bind to proteins, is a central selenium species in the pathways leading to the formation and degradation of selenium proteins. Selenide is also formed from selenite by reduction via glutathione. This reaction occurs in rat (Gasiewicz and Smith 1978) and human (Lee et al. 1969) red blood cells, as well as in human plasma containing added glutathione (Mas and Sarker 1989).

Selenocysteine can also be metabolized to selenide. This reaction requires a specific enzyme, selenocysteine β-lyase, which catalyzes the decomposition of selenocysteine to alanine and hydrogen selenide. The enzyme requires pyridoxal 5-phosphate as a cofactor. In humans, the highest levels of selenocysteine β-lyase activity are found in the liver, followed by the kidney, heart, adrenal gland, and muscle (Daher and Van Lente 1992). In mice orally exposed to selenocysteine, an intermediate metabolite selenocysteine-glutathione selenyl sulfide is formed in the small intestine and transported to the liver via the blood plasma (Hasegawa et al. 1995, 1996a). This compound can be nonenzymatically reduced by excess glutathion or enzymatically reduced by glutathione reductase in liver cytosol extracts to reform selenocysteine, which can be further metabolized.

Selenomethionine metabolism to selenide and the incorporation into selenium-specific proteins may occur by two pathways: metabolism to methane selenol and selenide or via selenocysteine. Evidence that the incorporation of selenium from selenomethionine into protein is by the transsulfuration pathway (methionine to cysteine) comes from studies of selenomethionine metabolism in lymphoblast cell lines deficient in cystathionine lyase and cystathionine synthetase, enzymes of the transsulfuration pathway (Beilstein and Whanger 1992). Deficiency in these enzymes greatly reduces the incorporation of selenomethionine into glutathione peroxidase.

Similar to other metals, selenium can be methylated, and the extent of methylation is dose-dependent. Dimethyl selenide is exhaled, and the trimethylselenonium ion is a major urinary metabolite of selenium. Methylation of selenium is a detoxification pathway that is especially important at high selenium doses.

Humans accidentally exposed to high levels of selenium have been reported to have a noticeable garlic odor of the breath, probably as a result of excretion of dimethyl selenide in expired air (Bopp et al. 1982; Wilbur 1980). Garlic odor of the breath has been noted in humans following ingestion of toxic levels of sodium selenate (Civil and McDonald 1978) and following inhalation of elemental selenium dust or selenium dioxide (Glover 1970).

In human populations with sufficient levels of selenium, dietary selenium is apparently partitioned into a selenite-exchangeable storage pool and a selenite-nonexchangeable storage pool. The selenite-exchangeable pool shows saturation kinetics. After this pool is filled, dietary selenium as seleno-methionine may be the primary determinant of selenium bioavailability and serum selenium concentrations (Meltzer et al. 1990, 1992). Data from both humans and Rhesus monkeys indicate that the selenium concentration in glutathione peroxidase is independent of the form of selenium administered and suggest a metabolic saturation at average intake rates (Butler et al. 1990; Meltzer et al. 1990).

In macaques that were orally administered doses of 0.025–0.3 mg selenium/kg as L-selenomethionine for up to 30 days, both erythrocyte selenium and glutathione peroxidase–specific activity showed a delay before increasing in a dose-related manner (Hawkes et al. 1992). At 0.15 and 0.3 mg selenium/kg, glutathione peroxidase–specific activity in erythrocytes continued to increase for 15 days after cessation of treatment and remained elevated through the end of the study (40 days after the end of treatment). The investigators attributed this effect to an initial deposition of selenium into a nonspecific pool (such as substitution for methionine in serum proteins), followed by slow release into the erythrocyte. Wistar rats also show incorporation of selenomethionine into proteins (Behne et al. 1991).

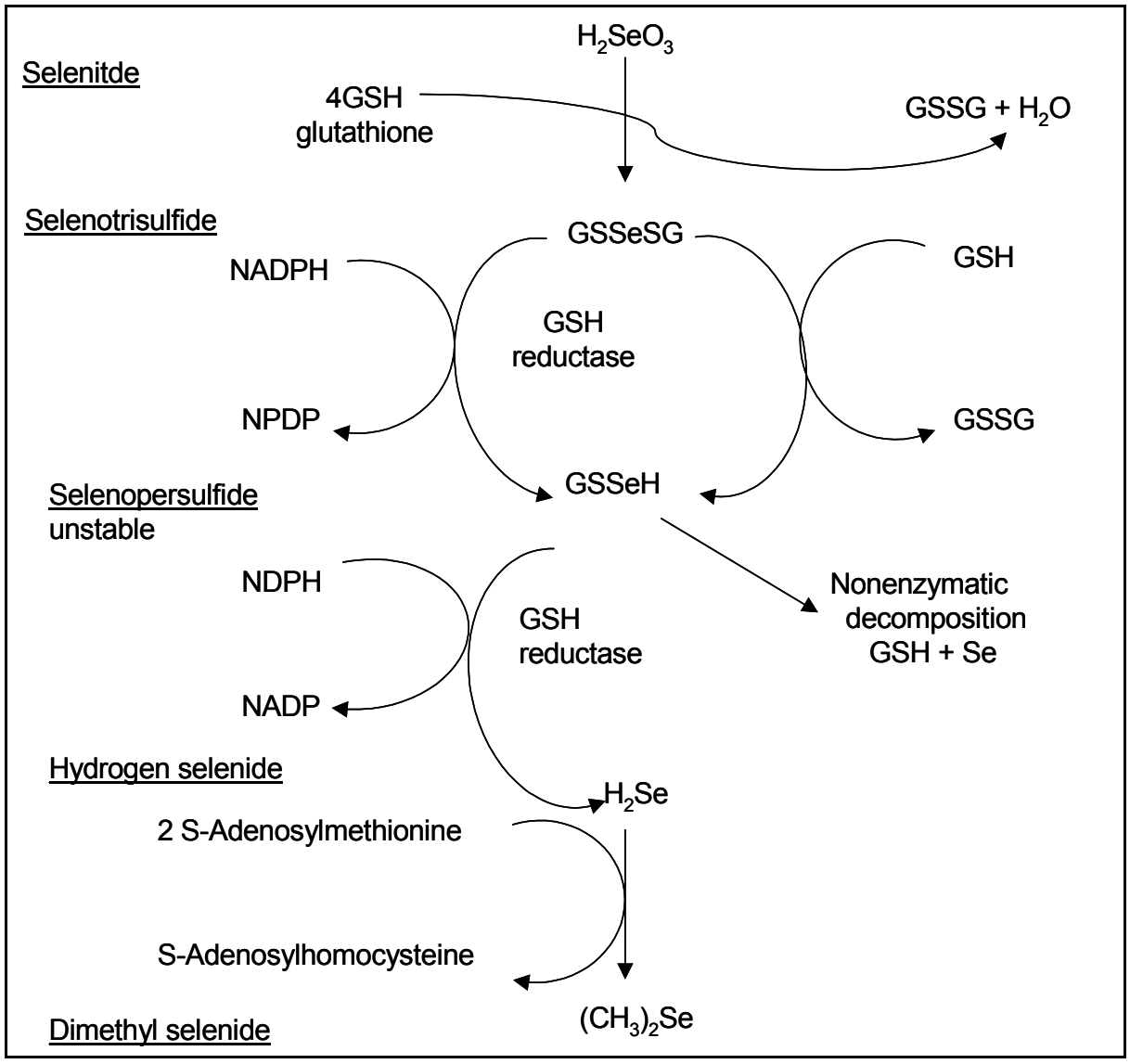
In rats, dimethyl selenide has been identified as the primary respiratory metabolite following injection of sodium selenite or sodium selenate (Hirooka and Galambos 1966b) and appears to be produced in the liver (Nakamuro et al. 1977). In mice, dimethyl selenide and dimethyldiselenide have been detected in expired air following the addition of unspecified amounts of sodium selenite, D,L-selenomethionine, or D,L-selenocystine to their drinking water (Jiang et al. 1983). A third unidentified volatile selenium compound was detected in expired air of the mice following D,L-selenomethionine injection (Jiang et al. 1983).

In rats, the trimethylselenonium ion has been identified as the predominant urinary metabolite following intraperitoneal administration of sodium selenite (Byard and Baumann 1967), sodium selenate, selenomethionine, selenocystine, or methylselenocysteine, or following ingestion of seleniferous wheat (Palmer et al. 1970). A total of 30.8% of the urinary selenium was in the form of trimethylselenonium after administration of 15 ppm selenium in wheat. Another major selenium metabolite that appeared in the urine more slowly than the trimethylselenonium ion was identified chromatographically, but the chemical structure of that metabolite was not defined (Palmer et al. 1970).

Similarly, the trimethylselenonium ion was the major urinary metabolite of selenium excreted by rats after intraperitoneal injection of either methylselenocysteine (4 mg/kg) or selenocysteine (3 mg/kg) (Palmer et al. 1970). The amounts of trimethylselenonium ion excreted were 50.6 and 49.7% of the total urinary metabolites after methylselenocysteine and selenocysteine administration, respectively. In both cases, urinary metabolism accounted for only 10–15% of the administered dose. As selenium was not measured in feces or expired air, recovery of the dose was incomplete. In a review of the metabolic pathways resulting in the production of dimethyl selenide from selenite in rodents, Ganther (1979) indicated that reduction of selenite or selenate to dimethyl selenide requires glutathione and the methylating agent *S*-adenosylmethionine. NADPH, coenzyme A, ATP, and magnesium (II) salts are also required to provide optimal conditions for this reaction (Ganther 1979). Ganther (1971) and Hsieh and Ganther (1975) found that selenite initially reacts nonenzymatically with glutathione to form a selenotrisulfide derivative. The selenotrisulfide is then reduced nonenzymatically in the presence of glutathione or enzymatically by glutathione reductase in the presence of NADPH to a selenopersulfide (GSSeH). The selenopersulfide is unstable and decomposes to glutathione and selenium or is enzymatically reduced by glutathione reductase in the presence of NADPH to hydrogen selenide (Ganther 1971; Hsieh and Ganther 1975). Hydrogen selenide can be methylated by *S*-adenosylmethionine in the presence of selenium methyltransferase to form dimethyl selenide (Figure 3-5).

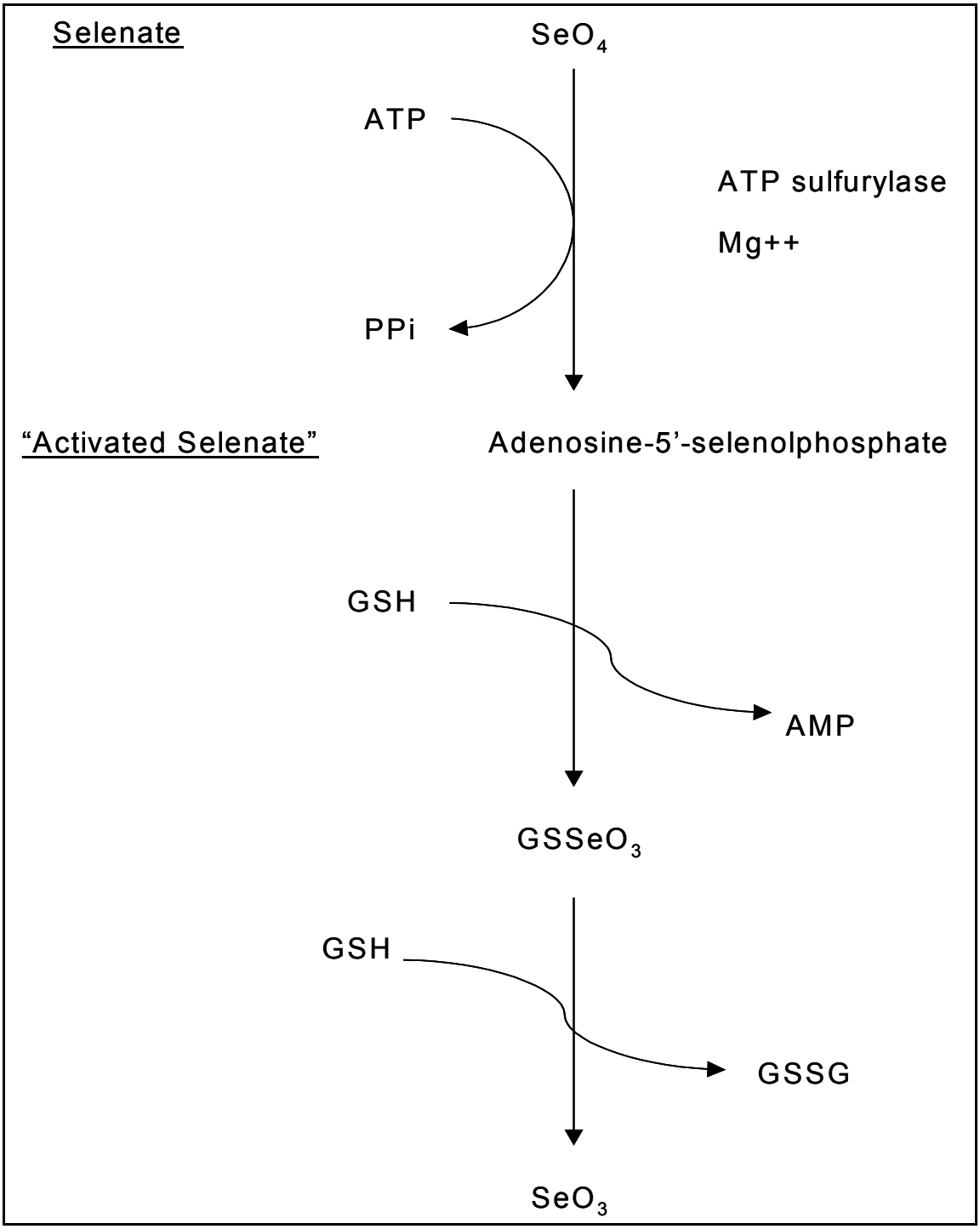
Selenate apparently is not converted to dimethyl selenide as readily as is selenite. Studies of selenate metabolism are limited in mammals, but studies using bacteria indicate that selenate must be activated prior to conversion to selenite (Bopp et al. 1982). Dilworth and Bandurski (1977) demonstrated that in the presence of ATP, magnesium (II) salts, and ATP-sulfurylase, yeast could convert selenate to eventually yield selenite (Figure 3-6). Data regarding the metabolism of selenium sulfide after administration to humans or other animals were not located in the literature.

Figure 3-5. Proposed Pathway for Formation of Dimethyl Selenide from Selenite in Animals*



*Adapted from Hsieh and Ganther 1975 and Ganther 1971

Figure 3-6. Activation and Reduction of Selenate to Selenite in Yeast *Saccharomyces cerevisiae



*Adapted from Dilworth and Bandurski 1977

3.4.4 Elimination and Excretion

Excretion of selenium can occur in the urine, feces, and expired air (Griffiths et al. 1976; Hawkes et al. 1992, 1994; Lathrop et al. 1972; McConnell and Roth 1966; Thomson and Stewart 1974). Sweat is a minor pathway of selenium excretion in humans (Levander et al. 1987). Moreover, the initial rate of excretion appears to be dose dependent (Lathrop et al. 1972; McConnell and Roth 1966; Thomson and Stewart 1974). Some researchers have found that urinary excretion and fecal excretion of selenium are similar, with each route contributing approximately 50% of the total output (Stewart et al. 1978). However, the proportion excreted via each route seems dependent on several factors, including the level of exposure, the time since exposure, and the level of exercise. Lactating women and subjects depleted of selenium and have decreased excretion of selenium in the urine and feces (Martin et al. 1989a, 1989b; Moser-Veillon et al. 1992). At high selenium exposure levels, excretion of selenium in expired air becomes more significant (McConnell and Roth 1966; Olson et al. 1963).

3.4.4.1 Inhalation Exposure

Following acute inhalation exposures to selenium compounds, humans excrete some of the absorbed dose in the expired air (Glover 1970), but no studies were located that actually quantified the rate of excretion or identified the selenium compounds in the expired air of humans.

3.4.4.2 Oral Exposure

Several human studies have indicated that the rate of urinary excretion is most rapid in the first 24 hours following oral administration or intravenous injection of sodium selenite (Kuikka and Nordman 1978; Thomson and Stewart 1974). Thomson and Stewart (1974) found <6% of a trace dose (0.01 mg selenium) of orally administered sodium selenite was excreted in the urine within 24 hours of administration, whereas 64–73% of a 1-mg dose of selenium was excreted in the first 24 hours (Thomson 1974). Thomson et al. (1977) also found that a lower proportion of the selenium from an oral dose of 0.1 mg selenium administered as selenomethionine was excreted in the 24-hour urine than from a larger dose (1.0 mg selenium). Thus, when higher amounts of selenium are administered, a higher proportion of the selenium is excreted in the urine during the first 24 hours following exposure.

Decreasing urinary or fecal excretion appears to be the homeostatic mechanism by which the body retains greater amounts of selenium. Martin et al. (1989a) observed greater retention of selenium by individuals

maintained on a selenium-deficient diet. This increase in retention was correlated with a decrease in fecal elimination. Similarly, the increased retention of selenium from selenomethionine compared to selenite was correlated with decreased elimination (Swanson et al. 1991). Lactating women have a greater retention of selenium from selenomethionine compared to selenite and a decreased urinary elimination (Moser-Veillon et al. 1992). Muscle activity seems to influence urinary excretion of selenium as demonstrated by the doubling of selenium concentration in the urine of women following vigorous exercise (Oster and Prellwitz 1990).

Less information is available regarding the elimination of selenium in the feces of humans than in the urine of humans. However, levels of fecal excretion of selenium have been reported to be similar to levels of urinary selenium excretion when dietary levels of selenium are not excessive (Patterson et al. 1989). Over a 14-day period, Stewart et al. (1978) found urinary elimination of selenium to average 0.013 mg selenium/day and fecal elimination of selenium to average 0.011 mg selenium/day in four New Zealand women exposed to 0.024 mg selenium/day in their normal diets. Levander and Baumann (1966a, 1966b) have suggested that some of the selenium in the feces can be attributed to biliary excretion. Higher dietary levels of selenium appear to enhance fecal elimination (Gortner and Lewis 1939).

In humans, whole body retention studies following oral administration of sodium selenite have indicated that selenium elimination is triphasic (Thomson and Stewart 1974). During the initial phase, which lasted about 1 week, elimination of selenium was rapid, with a half-life of approximately 1 day (Thomson and Stewart 1974). In the second phase, which also lasted approximately 1 week, selenium elimination was slower, with a half-life of 8–9 days. In the third phase, selenium elimination was much slower, with a half-life estimated to be 115–116 days. The first two elimination phases correspond to the fecal elimination of nonabsorbed selenium and the urinary excretion of absorbed but unutilized selenium (Thomson and Stewart 1974). Selenomethionine elimination is also triphasic; however, its terminal half-life is longer than that of sodium selenite. The average half-lives of selenomethionine for the three phases were measured to be approximately 0.4–2, 5–19, and 207–290 days, respectively (Griffiths et al. 1976).

An examination of elimination data from 44 pigs exposed to excess selenium as sodium selenite in feed was found to fit a one-compartment model of selenium elimination (Davidson-York et al. 1999). Serum selenium levels were monitored over a period of 46 days beginning 1–14 days after termination of exposure to the feed containing excess selenium. Data were not adequate to depict the initial distribution phase, but a geometric mean elimination half-life of 12 days was calculated. It is likely that the period of

elimination included in this study corresponds to the second phase described by Thomson and Stewart (1974).

The chemical form of selenium may play a role in determining how rapidly selenium is excreted in the urine. In rats, the rate of urinary excretion of selenium has been found to be greater following oral administration of sodium selenite than of selenomethionine (Thomson and Stewart 1973). A comparison of excretion of selenium by selenium-depleted rats after oral administration of sodium selenate, selenomethionine, or methyl selenocysteine (from high-selenium broccoli) found that excretion of selenium from methyl selenocysteine or selenomethionine was significantly lower than from sodium selenate; further, that there was no significant difference between secretion of selenium from methyl selenocysteine and selenomethionine (Finley 1998). This may contribute to the greater retention of selenium from selenomethionine, than from inorganic selenium (Martin et al. 1989a). However, another study of excretion of selenium from rats fed selenium as either sodium selenite or selenomethionine found that excretion of selenium increased with administered dose, but was similar for both forms of selenium (Shiobara et al. 1998).

As exposure to oral L-selenomethionine increased in macaques, the amount of selenium eliminated in the urine/day increased, as did the maximum rate of urinary excretion. However, the percentage of administered dose appearing in the urine decreased with an increase in dose (Hawkes et al. 1994).

3.4.4.3 Dermal Exposure

No studies were located regarding the excretion of selenium by humans or other animals after dermal exposure to elemental selenium or selenium compounds.

3.4.4.4 Other Routes of Exposure

Whole body retention studies in sheep following injection of selenium have indicated that selenium excretion in animals follows a triexponential profile (Blodgett and Bevill 1987b; Ewan et al. 1967). In a 2-week study, Blincoe (1960) estimated the half-life for ^{75}Se in rats following intraperitoneal injection of ^{75}Se-labeled sodium selenite (0.93 mg selenium/kg). Initially, the excretion of selenium was rapid, with a half-life of approximately 0.8 day; the second phase of excretion was slower, with a half-life of 13 days. These results parallel the initial phases of selenium excretion seen in humans. The abbreviated duration of the Blincoe (1960) study did not permit the determination of a terminal elimination phase half-life. In

rats, Ewan et al. (1967) found the final phase of elimination of selenium following a single subcutaneous injection of sodium selenite to be dose independent (from 0.008 mg selenium/kg to 2 mg selenium/kg), with a half-life of 65–78 days. Blodgett and Bevill (1987b) found the elimination rate of selenium in sheep during the second phase following a single intramuscular injection of sodium selenite to be dose dependent, with larger doses resulting in longer half-lives (i.e., doses of 0.4, 0.6, 0.7, or 0.8 mg selenium/kg resulting in half-lives for selenium elimination of 6.3, 8.8, 15.1, and 20.4 hours, respectively). The reasons for the decreasing elimination rate with increasing dose during the second phase is not clear.

Dietary levels of selenium and the individual's selenium nutritional status are the most important factors that influence the route and rate of selenium excretion. Selenium excretion in expired air is only significant when exposures to selenium are high. Rats injected subcutaneously with sodium selenite at doses of 2.2–5.4 mg selenium/kg excreted 41–62% of the administered selenium in exhaled air, whereas rats injected with sodium selenite at doses of 0.005–0.9 mg selenium/kg excreted only 0.2–11% of the administered selenium in expired air (McConnell and Roth 1966; Olson et al. 1963). As the amount of administered sodium selenite increased, the percent of the administered selenium excreted in the urine decreased (from approximately 22–33% of the administered selenium at doses of 0.005–0.9 mg selenium/kg to 3–14% of the administered selenium at doses of 3.1–5.4 mg selenium/kg) (McConnel and Roth 1966). Selenium in the feces was not measured in this study. Burk et al. (1972) found that as the dietary level of sodium selenite was increased, a larger proportion of an injected tracer dose of selenium (as sodium selenite) was excreted. At a dietary level of 0.005 mg selenium/kg, approximately 60% of the injected selenium had been excreted in the first 35 days following administration. At a dietary level of 0.05 mg selenium/kg, over 94% of the injected selenium had been excreted over the same period of time.

In experimental animals, other factors that can cause an increase in selenium levels in expired air are higher dietary levels of selenium, protein, or methionine (Ganther et al. 1966). Phenobarbital induction of microsomal enzymes has also led to increased exhalation of selenium following intravenous administration of sodium selenite (Sternberg et al. 1968).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for

many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

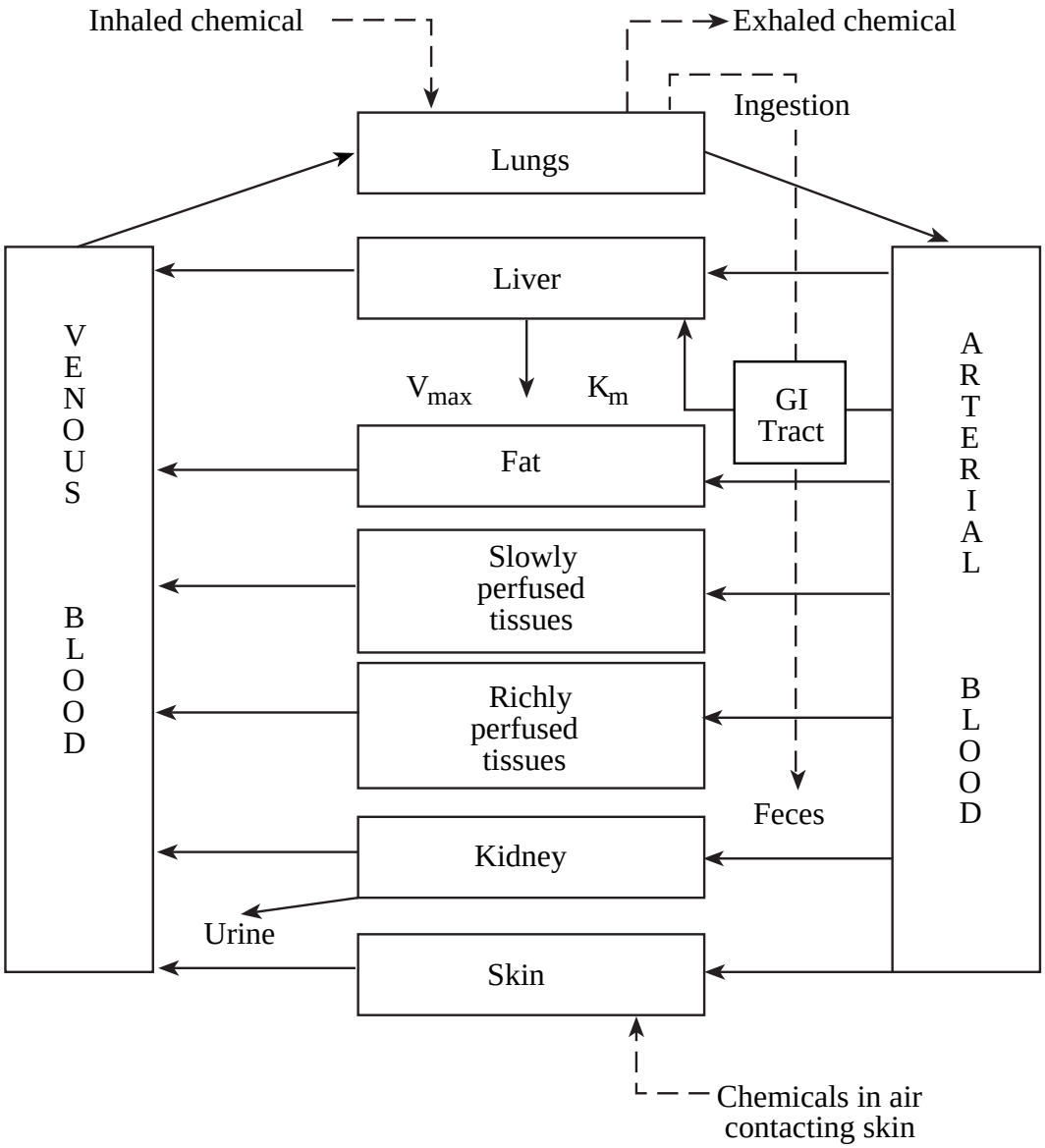
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-7 shows a conceptualized representation of a PBPK model.

Two models for selenium were located in the literature. Patterson and coworkers (Patterson and Zech 1992; Patterson et al. 1989, 1993) have developed compartmental models of the kinetics of selenium orally administered as selenite or selenomethionine in adult humans.

Patterson et al. (1989) Selenite Model

Description of the model. Patterson and coworkers (Patterson and Zech 1992; Patterson et al. 1989, 1993) developed a compartmental model of the kinetics of ingested selenite in adult humans based on data from human subjects who consumed a single oral dose of 200 μg ^{74}Se as selenite. The model assumes that 84% of the administered selenium is absorbed and that absorption is rapid. Absorbed selenite is assumed to distribute to six compartments: gastrointestinal tract, plasma, hepatopancreatic/ lymphatic system, liver/pancreas, bile, and tissues (Figure 3-8). Unabsorbed selenium is excreted in the feces. Absorption occurs from the gastrointestinal compartment (probably the small intestine, but also possibly the stomach) into a rapidly turning-over pool (the intestinal cells or enterocytes) from which it leaves by two pathways. The central compartment is represented as four kinetically distinct plasma pools, P1 (the portal circulation), P2 (before passage through the liver), P3 (after passage through the liver), and P4 (after passage through the tissues). In the first pathway, selenium enters P1. The second pathway is to a liver/pancreatic compartment. Transport into and out of P1 is very rapid ($T_{1/2}$ approximately 0.36 hours) and this may represent selenium in the portal circulation passing through the liver before appearing in P3, but not removed in the first pass. The second pathway is via the hepatopancreatic/lymphatic system compartment to a second plasma pool (P2). Appearance of selenium in P2 is delayed ($T_{1/2}$ approximately 0.55 hours), representing the time needed to move through

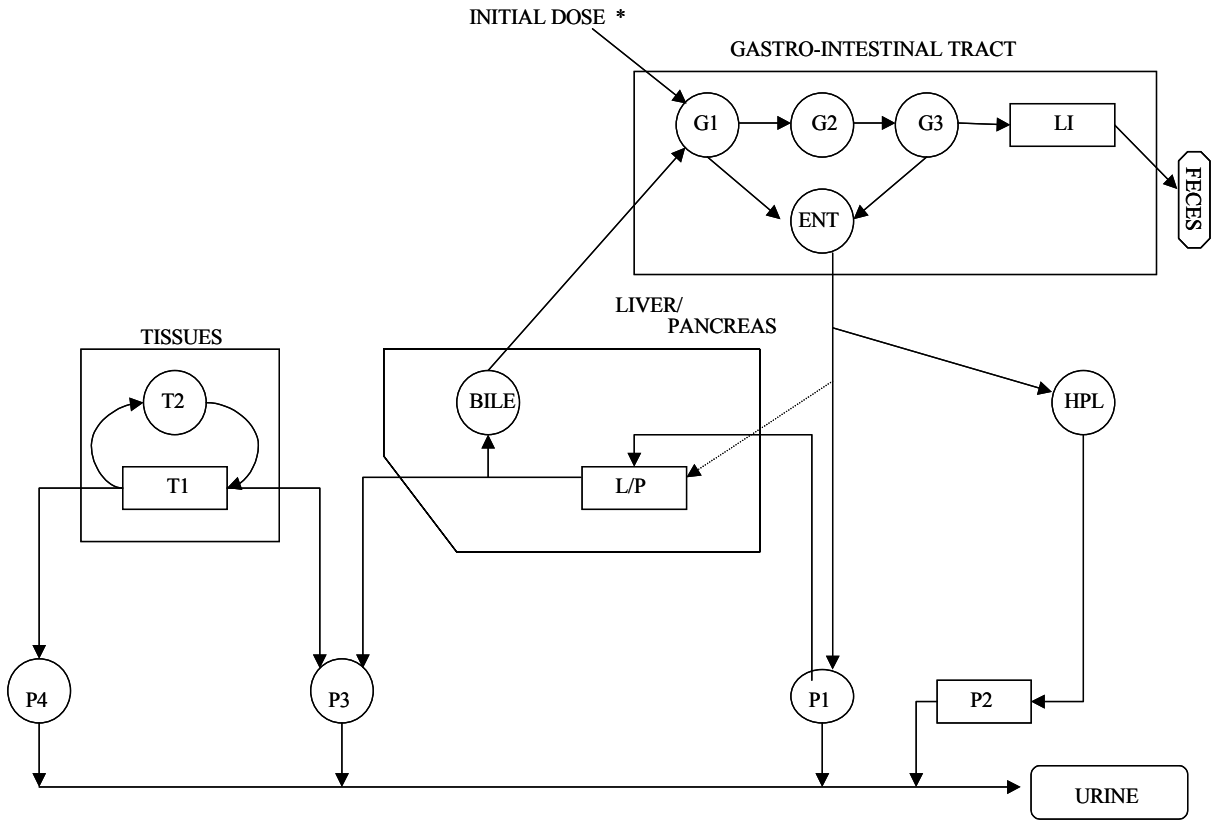
Figure 3-7. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Figure 3-8. Selenite Model, a Kinetic Model for Selenite Metabolism



The arrow with an asterisk indicates the site of entry of the oral Se tracer. Arrows between compartments represent pathways of fractional transport. Compartments depicted as rectangles represent delays. Compartments G1, G2, G3, 3 gut compartments, probably the small intestine; ENT, enterocytes (intestinal cells); HPL, compartment in hepato-pancreatic subsystem or lymphatic system; L/P, liver and pancreas; LI, large intestine; T1, T2, peripheral tissues, e.g., skeletal muscle, bone, kidney. Feces and urine compartments are drawn in the shape of test tubes to represent fractional (single) collections. The model includes absorption distributed along the gastrointestinal tract, enterohepatic recirculation, four kinetically distinct plasma pools, P1–P4, a subsystem consisting of liver and pancreas, and a slowly turning-over tissue pool.

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the hepatopancreatic/lymphatic system compartment. From the two plasma pools (P1 and P2), selenium can be excreted in the urine ($T_{1/2}$ approximately 3.94 and 1.96 hours, respectively) or it can move into the liver/pancreas compartment. After a delay of 4–6 hours, the selenium leaves the liver/pancreas either to a bile compartment ($T_{1/2}$ approximately 0.13 hours) and thence to the gut (G1) for excretion in feces or to a third plasma pool (P3) ($T_{1/2}$ approximately 0.19 hours). From P3, selenium can be excreted in the urine ($T_{1/2}$ approximately 4.15 hours) or can move into a large, slowly turning-over tissue compartment. Finally, selenium is transferred very slowly ($T_{1/2}$ approximately 1.27 hours) from the tissues (probably final metabolic products) to a fourth plasma pool (P4) and hence to the urine ($T_{1/2}$ approximately 6.54 hours).

Validation of the model. The extent to which this model has been validated is not described in Patterson and coworkers (Patterson and Zech 1992; Patterson et al. 1991, 1993).

Risk assessment. The model was designed to simulate the pharmacokinetics of selenium orally administered as selenite to humans as a preparation for a larger anticancer supplementation study jointly undertaken by the National Cancer Institute (NCI) and the U.S. Department of Agriculture (USDA) (Patterson and Zech 1992; Patterson et al. 1991, 1993).

Target tissues. The model is designed to simultaneously account for the appearance and disappearance of selenium in plasma, urine, and feces after administration of a single oral dose of ^{74}Se as selenite (Patterson and Zech 1992; Patterson et al. 1991, 1993).

Species extrapolation. The model is designed for applications to human dosimetry and cannot be applied to other species without modification.

Interroute extrapolation. The model is designed to simulate oral exposures to selenite and cannot be applied to other routes of exposure without modification.

Extrapolation to other forms of selenium. The model is designed to simulate oral exposures to selenite and cannot be applied to other forms of selenium without modification.

Swanson et al. (1991) Selenomethionine Model

Description of the model. Swanson and coworkers (Patterson et al. 1993; Swanson et al. 1991) produced a model for ingested selenomethionine in adult humans based on data from human subjects who consumed a single oral dose of 200 μg ^{74}Se as selenomethionine and the model of the kinetics of ingested selenite described above. Four major changes (indicated by bold lines in Figure 3-9) were made to the selenite model to achieve an adequate fit to the selenomethionine data: (1) the amount of label absorbed into the enterocyte was increased (the absorption of ^{74}Se was 98% for selenomethionine compared with 84% for selenite), (2) the amount of label removed from the plasma in the first pass through the liver was increased, (3) a pathway from P4 back to the liver was added, providing for conservation and reutilization of amino acids (estimated 95% of material from P4 is recycled), and (4) a second tissue subgroup was added to the model and rate constants were adjusted so that the subgroups had different turnover times.

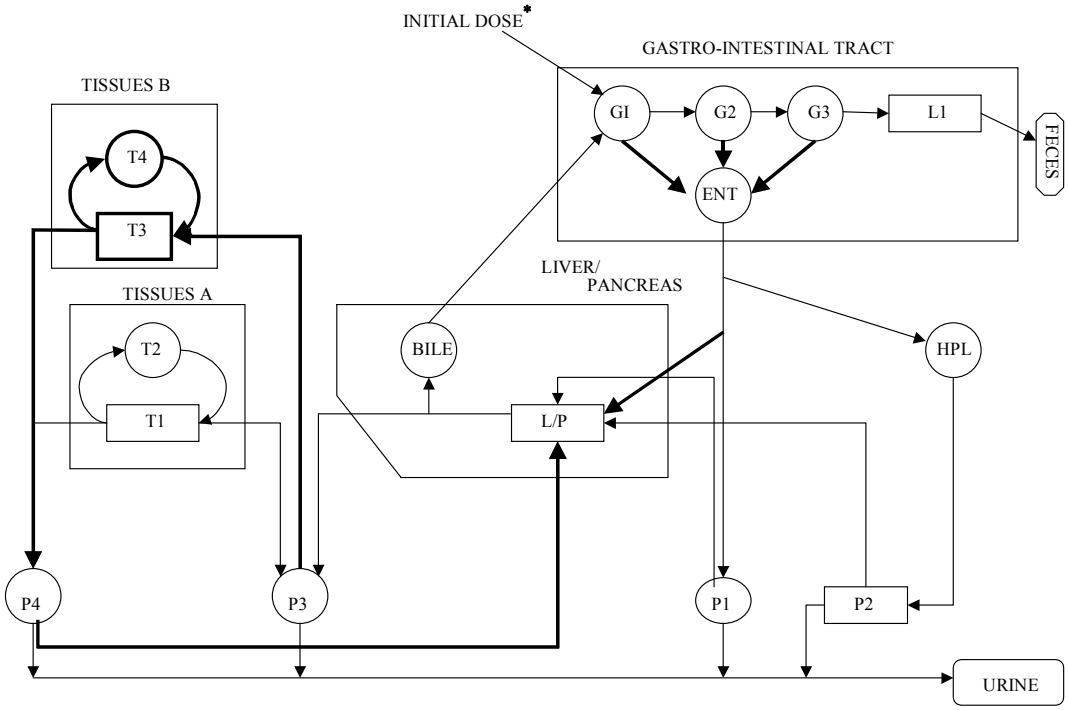
The most important differences between the selenite and selenomethionine models lie in the turnover times. The estimated turnover times in the plasma, liver/pancreas, and tissues are shorter for selenomethionine than for selenite, but the estimated turnover time for the whole body is more than twice as long for selenomethionine as for selenite. This is probably because selenite is not recirculated, whereas selenomethionine is extensively recycled, passing through the individual organs and tissues many times before being excreted.

Validation of the model. The extent to which this model has been validated is not described by the authors (Patterson et al. 1993; Swanson et al. 1991).

Risk assessment. The model was designed to simulate the pharmacokinetics of selenium orally administered as selenomethionine to humans as a preparation for a larger anti-cancer supplementation study jointly undertaken by the NCI and the USDA (Patterson et al. 1993; Swanson et al. 1991).

Target tissues. The model is designed to simultaneously account for the appearance and disappearance of selenium in plasma, urine, and feces after administration of a single oral dose of ^{74}Se as selenomethionine (Patterson et al. 1993; Swanson et al. 1991).

Figure 3-9. Selenomethionine Model, a Kinetic Model for Selenomethionine Metabolism



The arrow with an asterisk indicates the site of the oral Se tracer. Arrows between compartments represent pathways of fractional transport. Compartments depicted as rectangles represent delays. G1, G2, G3, three gut compartments, probably small intestine; ENT, enterocytes (intestinal cells); HPL, compartment in hepatopancreatic subsystems or lymphatic system; L/P, liver and pancreas; LI, large intestine; T1, T2, T3, T4, peripheral tissues, e.g., skeletal muscle, bone, kidney. Feces and urine along the gastrointestinal tract, enterohepatic recirculation, four kinetically distinct plasma pools, P1–P4, a subsystem consisting of the liver and pancreas, two tissue subsystems that are slowly turning-over, and a pathway for reutilization of selenium metabolites from peripheral tissues. The bold lines indicate the major modifications to the Selenite Model (Figure 3-8).

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Species extrapolation. The model is designed for applications to human dosimetry and cannot be applied to other species without modification.

Interroute extrapolation. The model is designed to simulate oral exposures to selenomethionine and cannot be applied to other routes of exposure without modification.

Extrapolation to other forms of selenium. The model is designed to simulate oral exposures to selenomethionine and cannot be applied to other forms of selenium without modification.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

As discussed in Section 3.4.1, selenium is readily absorbed by inhalation or ingestion when present in any of several compounds. Inhalation and oral absorption are extensive, although the rate of absorption varies depending on the form of selenium (Medinsky et al. 1981a; Moser-Veillon et al. 1992; Swanson et al. 1991; Weissman et al. 1983; Young et al. 1982). Oral bioavailability is generally independent of the exposure level, but may be increased in some selenium-deficient individuals (Griffiths et al. 1976; Martin et al. 1989a; Thomson 1974; Thomson et al. 1977). Selenate and selenomethionine appear to be absorbed by the intestine largely unchanged, while selenite and selenocysteine are metabolized during absorption (Hasegawa et al. 1995, 1996a; Spencer and Blau 1962; Whanger et al. 1976, 1996). No evidence of significant dermal absorption of selenium by humans was located, although mice can absorb topically-applied selenomethionine (Burke et al. 1992b).

Absorbed selenium is carried throughout the body in the blood, eventually being distributed to all tissues. Injection studies in humans have shown that after selenium enters the blood, it rapidly becomes protein-bound (Burk 1974; Hirooka and Galambos 1966a), while *in vitro* studies have shown that selenite is accumulated in erythrocytes via an active transport mechanism (Lee et al. 1969). Selenium is an essential element and is incorporated into selenoproteins (e.g., glutathione peroxidase, iodothyronine deiodinases) as selenocysteine. Most studies report similar distribution patterns for selenium, regardless of the form in which it was administered; however, the concentration reached is generally higher for doses delivered as an organic forms of selenium than for the same dose delivered as an inorganic form (Behne et al. 1991; Butler et al. 1990; Gronbaek and Thorlacius-Ussing 1992; Ip and Hayes 1989; Salbe and Levander 1990b; Shiobara et al. 1998; Zi-Jian Jie 1992). In humans, the highest levels of selenium are found in the

liver and kidney (see Table 3-6 for normal levels of selenium in human tissues). Selenomethionine is not synthesized by humans, but can be incorporated into proteins in the place of methionine; because of this, selenomethionine is retained for a longer time within the body than inorganic forms, and it may therefore represent a storage form of the element.

Excretion of selenium by humans occurs in the urine, feces, expired air, and sweat, but urine and feces are the major routes of elimination. Some of the selenium in feces may be due to bilary excretion (Levander and Baumann 1966a, 1966b). Elimination is reduced in selenium-deficient individuals and may represent a mechanism by which selenium levels are regulated (Martin et al. 1989a; Swanson et al. 1991). Methylation is an important mechanism of detoxification for selenium; dimethyl selenide is exhaled, and the trimethylselenonium ion is the major urinary metabolite of selenium. Experiments in mice suggest that the hepatic toxicity of selenium may be at least partly due to depression of selenium methylation in the liver, resulting in the accumulation of excess selenides (Nakamuro et al. 2000).

3.5.2 Mechanisms of Toxicity

Little is known about the specific biochemical mechanism(s) by which selenium and selenium compounds exert their acute toxic effects. Long-term effects on the hair, skin, nails, liver, and nervous system are also well documented, and a general theory has been developed to explain the toxicity of exposure to excess selenium, as discussed below. Generally, water-soluble forms are more easily absorbed and are generally of greater acute toxicity. Mechanisms of absorption and distribution for dermal and pulmonary uptake are unknown and subject to speculation, but an active transport mechanism for selenomethionine absorption in the intestine has been described (Spencer and Blau 1962). The mechanisms by which selenium exerts positive effects as a component of glutathione peroxidase, thioredoxin reductase, and the iodothyronine 5'-deiodinases are better understood, but the roles of other selenium-containing proteins in mammalian metabolism have not been clarified.

One theory of the mechanism of acute selenium toxicity concerns inactivation of the sulfhydryl enzymes necessary for the oxidative reactions in cellular respiration (Lombeck et al. 1987; Mack 1990; Shamberger 1981). Acute toxic effects, such as pulmonary edema, can result in respiratory failure and death. The lung, however, does not appear to be a target organ at levels of exposure less than the occupational permissible exposure limits (PELs) or threshold limit values (TLV).

Selenium can replace sulfur in biomolecules, especially when the concentration of selenium is high and the concentration of sulfur is low in the organism. This substitution may be a mechanism of selenium toxicity (Stadtman 1983). Selenocysteine is specifically found in some proteins (e.g., glutathione peroxidase); selenomethionine appears to randomly substitute for methionine in protein synthesis. This appears to be an additional mechanism for intermediate or chronic duration toxicity (Stadtman 1983; Tarantal et al. 1991). Skin, hair, and nail damage are significant indicators of chronic selenium overexposure. Although the mechanism causing these integumentary effects is not known, it is probably related to the high selenium concentrations in these tissues as a consequence of the substitution of selenium for sulfur in certain amino acids. Researchers have concluded that the nails and hair are routes to excrete excess selenium (Yang et al. 1989b). Other studies suggest that selenium may also influence thyroid hormone function via the deiodinase enzymes (Brätter and Negretti De Brätter 1996; Hawkes and Keim 1995).

3.5.3 Animal-to-Human Extrapolations

No studies were located that specifically examined species-related differences in selenium pharmacokinetics. Similar patterns of absorption, distribution, and elimination have been reported for human and animal systems and the dermal, endocrine, and neurological effects of chronic exposure in humans are similar to those reported for animals exposed to very high doses of selenium. However, species-specific differences in toxicity are present (e.g., the main effect of selenium toxicity in rodents is damage to the liver, which is not observed in humans) and this may represent evidence of underlying differences in how selenium is metabolized.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Thomas (1992) and again by Colborn (1993), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its

deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Mayr et al. 1992; Livingston 1978). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997c). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Hoel et al. 1992; Giwercman et al. 1993; Berger 1994).

Selenium is a component of all three members of the deiodinase enzyme family, the enzymes responsible for deiodination of the thyroid hormones (Kohrle 1994; St. Germain and Galton 1997). The deiodinases contain a selenocysteine at the active site, which is required for catalytic activity. There are three types of deiodinases and they differ in terms of tissue distribution, reaction kinetics, efficiency of substrate utilization, and sensitivity to inhibitors. The first to be recognized as a selenoprotein was type I iodothyronine 5'-deiodinase which converts the prohormone thyroxine (T4) to the active form, triiodothyronine (T3) and to date, studies of the effects of excess selenium have focused on this protein. Under normal circumstances the human thyroid produces only 20–30% of its hormone as T3; the remainder is T4 (a minute amount of reverse T3 (rT3) is also produced), which is largely converted to active T3 by type I deiodinase located within the liver, euthyroid pituitary, kidney, thyroid, and brain. Type I deiodinase is a membrane bound protein and, thus, its activity has not been directly measured in studies of humans supplemented with selenium. Human studies have instead measured serum levels of T3, rT3, T4, and TSH.

Two human studies have demonstrated a decrease in T3 levels in response to increased dietary selenium although the hormone levels remained within the normal human range (Brätter and Negretti De Brätter 1996; Hawkes and Keim 1995). The effect of increased dietary selenium on other thyroid hormones is unclear. No significant correlation between selenium intake and serum T4 or TSH levels was found in the study of Brätter and Negretti De Brätter (1996). While in the study of Hawkes and Keim (1995), TSH concentration increased in the high selenium group (+37%) and was significantly different relative to baseline levels ($p<0.06$). In a third study of the effects of selenium supplementation, New Zealanders with normally low selenium intake (unsupplemented intake of 28–29 μg/day), showed a reduction in T4 concentration in all groups after 20 weeks (Duffield et al. 1999). A significant inverse correlation was found between serum levels of selenium and TSH among fish consumers; however, it is not known if this population had a high selenium intake (Hagmar et al. 1998).

Male rats receiving diets supplying $0.05mg selenium/kg/day for 6–12 weeks has been shown to have reductions in type-I-deiodinase activity (Behne et al. 1992; Eder et al. 1995; Hotz et al. 1997). However, the levels of thyroid hormones in these animals have not shown a consistent pattern. Exposure to 0.055 mg selenium/kg/day as sodium selenite for 40 days produced a significant decrease in serum levels of T3 (Eder et al. 1995). While in another study, a dose of 0.09 mg selenium/kg/day as sodium selenate in food for 6 weeks produced a significant (~30%) increase in TSH (Hotz et al. 1997), and no significant changes in thyroid levels of T3 or T4 were found in rats receiving 0.105 mg selenium/kg/day as sodium selenite or 0.118 mg selenium/kg/day as L-selenomethionine for 3 months (Behne et al. 1992).

Many studies have documented reduced body weight gain in young animals treated with selenium compounds and abnormal weight loss in older animals (Grønback et al. 1995; Halverson et al. 1966; Harr et al. 1967; Jacobs and Forst 1981a; Nelson et al. 1943; NTP 1994; Johnson et al. 2000; Palmer and Olson 1974; Panter et al. 1996; Schroeder 1967; Tsunoda et al. 2000). There is evidence to suggest that these effects may be due in part to the interactions of selenium or selenium compounds with hormones that regulate normal growth and body weight. Reduced somatomedin C levels, reduced insulin-like growth factor–binding protein-3, and a reduction in growth hormone secretion in response to growth hormone releasing factor have been reported for rats exposed to sodium selenite in drinking water (Gronbaek et al. 1995; Thorlacius-Ussing et al. 1988).

No studies were located regarding adverse effects on human reproduction following oral exposure to elemental selenium or to selenium compounds. However, data from animal studies suggest that oral exposure to selenium may be associated with male infertility. Adverse effects associated with selenium

exposure include decreased sperm counts in rats and rabbits (El-Zarkouny et al. 1999; Kaur and Parshad 1994; NTP 1994), sperm abnormalities in rats and rabbits (El-Zarkouny et al. 1999; Kaur and Parshad 1994), testicular hypertrophy in rats (Turan et al. 1999a), and a significant reduction in serum testosterone in rabbits (El-Zarkouny et al. 1999). However, it is not clear what effect, if any, this had on the ability of the animals to reproduce, as chronic administration of selenate did not affect male fertility in rats or mice (Rosenfeld and Beath 1954; Schroeder and Mitchener 1971b).

Chronic exposure of mice and rats to otherwise nontoxic doses has been shown to reduce fertility and to markedly reduce the viability of the offspring of pairs that are able to conceive (Schroeder and Mitchener 1971b; Wahlstrom and Olson 1959b). Selenium exposure has been shown to alter the length of the estrous cycle in female mice (Nobunaga et al. 1979) and to alter the menstrual cycle in monkeys (Cukierski et al. 1989). Vaginal cytology of female rats provided with drinking water containing selenate or selenite indicated that the rats spent more time in diestrus and less time in proestrus and estrus than the controls (NTP 1994). However, it is not clear what effect, if any, this had on the ability of the animals to reproduce.

Fertility studies in mice, rats, and pigs have demonstrated reduced rates of conception after oral treatment with selenium as selenate or selenite (Rosenfeld and Beath 1954; Schroeder and Mitchener 1971b; Wahlstrom and Olson 1959b). Decreased conception rates and increased resorption rates have been reported for cattle, sheep, and horses fed diets naturally containing organic selenium compounds and exhibiting symptoms of selenosis (Harr and Muth 1972). An increased concentration of progesterone in the milk and an association of cystic ovaries with elevated blood selenium concentrations was observed in cows receiving selenium supplementation (Mohammed et al. 1991).

Other possible examples of endocrine disruption due to selenium exposure include pancreatic damage in sheep and rats fed selenium as sodium selenite, sodium selenate, or seliniferous wheat (Halverson et al. 1966; Harr et al. 1967; Smyth et al. 1990) and decreased plasma glucose (an insulin-like effects) in rats injected with sodium selenate. However, these are isolated reports and it is not clear what relevance they have for selenium toxicity in humans.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient

tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Selenium is known to be an essential micronutrient for humans and animals; therefore, inadequate as well as excessive selenium intake can cause adverse health effects. The Food and Nutrition Board of the National Research Council has established adequate intakes (AI) of 15–20 µg/day for infants based on the selenium content of milk of well nourished, but unsupplemented, mothers (NAS 2000). No data were available on which to base RDAs for children or adolescents and so the RDAs for children and adolescents are extrapolated from adult values. Studies of selenium deficient populations suggest that children are more susceptible to the effects of selenium deficiency and have the highest need for selenium of any individuals in the population (Chen et al. 1980; Yang et al. 1988).

Limited information is available on the toxicity of selenium in children, but the available information suggests that children may be less susceptible to toxic effects of selenium than adults. Most data come from children living in areas of chronic high dietary selenium intake (Yang et al. 1989a, 1989b). Children (aged 3–12 years) in a seleniferous area of China were found to have a significantly higher intake of selenium than the adults in their community, but a corresponding increase in blood levels of selenium appeared only in the children aged 7–12. When the incidence of selenosis in different age groups was examined, it was found that 97% of cases were older than 18 years, and no cases were observed in children below 12 years of age, even though selenium intakes per kg body weight and blood selenium levels in these age groups were found to be either higher than or equal to those of affected adults. One study of children living in a seleniferous area of Venezuela found a significant increase in the percentage of children showing lower than normal height compared with controls from a nonseleniferous area (Brätter et al. 1991a). However, these children also had very low intakes of zinc compared with controls (10–25% of controls) and it is likely that their reduced growth rate is due to inadequate intake of zinc. Another study that compared children from seleniferous and non-seleniferous areas of Venezuela

found slightly reduced height, weight, hemoglobin levels, and hematocrit values for the children from the seleniferous area (no statistical analysis was performed), although no clinical signs of selenosis were observed (Jaffe et al. 1972). However, the children from the seleniferous zone had a poorer diet, consumed less milk and meat, and had a greater incidence of intestinal parasites, which may account for the differences observed.

No adverse developmental effects of excess selenium have been reported for humans. Excess selenium is a demonstrated teratogen in birds (Franke and Tully 1935; Franke et al. 1936; Gruenwald 1958; Kahn and Gilani 1980; Palmer et al. 1973), but there is no clear evidence linking selenium exposures to developmental effects in mammals. Malformations have been reported for livestock that consumed naturally high seleniferous diets (Dinkel et al. 1963; Rosenfeld and Beath 1964), but it is not clear that these reports took into account consumption of other toxic range plants. Other studies of developmental effects in livestock receiving controlled diets with known amounts of selenium have generally not observed abnormalities, reduced birth weights, or increased mortality (Panter et al. 1995; Yaeger et al. 1998). Likewise, studies of laboratory animals have not observed developmental effects, except at levels of selenium administration that produce maternal toxicity (Bergman et al. 1990; Chiachun et al. 1991; Ferm et al. 1990; NTP 1996; Poulsen et al. 1989; Rosenfeld and Beath 1954; Schroeder and Mitchener 1971b; Thorlacius-Ussing 1990). In a teratology study of long-tailed macaques, no gross abnormalities or growth retardations were observed in fetuses from mothers administered doses that produced maternal toxicity.

No studies were located that compared pharmacokinetic properties of selenium in humans or animals of different ages. Selenium is transferred to fetuses via the placenta (Archimbaud et al. 1992; Choy et al. 1993; Hawkes et al. 1994; Jandial et al. 1976; Mahan and Kim 1996) and to infants via breast milk (Brätter and Negretti De Brätter 1996; Brätter et al. 1991b; Li et al. 1999; Michalke and Schramel 1998; Moser-Veillon et al. 1992; Rodríguez Rodríguez et al. 1999; Viitak et al. 1995; Yang 1989b). Studies of lactating women have shown a clear relationship between levels of selenium in the mother's diet and the concentration of selenium in her breast milk (Brätter et al. 1991b). However, there were no reports located of adverse effects in infants breast-fed by mothers in regions with high selenium diets.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to selenium are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by selenium are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in

the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 “Populations That Are Unusually Susceptible”.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Selenium

Selenium can be detected in the blood, feces, urine, hair, and nails of exposed individuals. Both selenium deficiency and excessive levels of selenium are associated with several disorders. For purposes of comparison, reported mean selenium concentrations in whole blood, blood constituents, urine, hair, nails, and the placenta for healthy individuals living in the United States and several other countries are listed in Table 3-7. The analytical methods used to measure selenium (described in Chapter 7) have improved, and the more recent studies may be more reliable. The values for the Chinese populations studied by Yang et al. (1983, 1989b) were those reported for individuals living in the selenium "adequate" regions included in the study. "Normal" selenium concentrations in blood constituents and other tissues in people from some countries (e.g., Finland) are generally lower than those in people living in the United States. In general, urinary excretion rates of 20–200 µg selenium/day are not associated with either selenium deficiency or toxicity (Sanz Alaejos and Diaz Romero 1993).

In the United States and other developed countries, hair selenium concentrations are not necessarily indicative of dietary exposure to environmental selenium. Users of therapeutic dandruff shampoos containing selenium sulfide may have high levels of selenium in their hair because the externally deposited selenium adsorbs to hair (Alfthan 1985). However, due to minimal levels of dermal absorption of selenium from shampoo, blood and urine levels are not significantly affected by selenium-containing shampoos (Howe 1979). Toenail samples have also been used as biomarkers of selenium exposure (Hunter et al. 1990a). Selenium levels in toenails were measured in volunteers who ate bread containing selenium for 1 year (Longnecker et al. 1993). During this time period, selenium in the large toenail did not reach a steady state, while a steady state was reached in the other toenails. After conclusion of the 1-year exposure, levels of selenium continued to decline until they reached baseline levels in 2 years.

At plasma and whole blood selenium concentrations of #0.10 mg selenium/L, a positive correlation has been reported between blood selenium levels and both erythrocyte and whole blood GSH-Px activity (Perona et al. 1977; Thomson 1977; Valentine et al. 1988). GSH-Px is an enzyme that acts as a scavenger of peroxides and protects cells from oxidative damage. However, whole blood selenium levels less than or equal to 0.10 mg selenium/L represent the lower end of the range of whole blood selenium concentrations reported by Allaway et al. (1968) for American males.

A correlation between blood selenium levels and GSH-Px activity was not observed when plasma and whole blood selenium levels were above 0.10 mg selenium/L. Therefore, GSH-Px activity is likely to be a biomarker for selenium deficiency but not for overexposure. Neve et al. (1988), on the other hand, found no relationship between erythrocyte or plasma GSH-Px activity levels and plasma selenium levels in a group of Belgian subjects with plasma selenium levels between 0.087 and 0.13 mg selenium/L. However, platelet GSH-Px activity levels did correlate with plasma selenium levels within this range (Neve et al. 1988). Valentine et al. (1980) measured the level of selenium in whole blood, urine, and hair of 33 residents from a Mexican village that consumed drinking water contaminated with selenium (0.026–1.8 mg selenium/L) from a uranium mill tailing pond. Blood levels ranging from 0.133 to 0.248 mg selenium/L, urine excretion rates ranging from 14.4 to 337.5 µg selenium/day, and hair selenium levels ranging from 0.02 to 1.98 µg selenium/g were not correlated with GSH-Px activity. In examining the relationship between selenium and GSH-Px activity, selenium-dependent GSH-Px activity must be distinguished from nonselenium-dependent GSH-Px activity (Edwards and Blackburn 1986).

Selenoprotein P which contains 10 selenocysteines, is the principal selenoprotein found in plasma (Sunde 1990). Selenoprotein P in plasma also does not continue to increase with increasing selenium and has been suggested as an alternative to GSH-Px as a biomarker for selenium status (Duffield et al. 1999; Huang et al. 1995). The function of selenoprotein P has still not been determined.

Field studies have used primarily blood or urine levels to indicate the degree of selenium exposure. Valentine et al. (1978) found a significant correlation between selenium levels in well water used for drinking and urine selenium excretion measured for 35 residents in a New Mexico community. However, no correlation was found between selenium levels in well water and the blood selenium levels of the 35 residents (Valentine et al. 1978). The correlation coefficients between the log of urine-selenium excretion (µg selenium/day) and the log of blood-selenium (mg selenium/L) with the log of the well water selenium concentration (mg selenium/L) were 0.57 ($p<0.01$) and 0.14 ($p>0.05$), respectively. The correlation coefficient between the log of hair selenium concentration (µg selenium/g) and the log of the well water selenium levels (mg selenium/L) was 0.45 ($p<0.01$).

Clinical symptoms have been associated with excessive blood, urine, and hair levels of selenium in exposed patients. Glover (1967) examined workers in a selenium rectifier factory and found that selenium levels in urine from workers exposed to selenium (annual averages from 1954 and 1958 range from 0.076 to 0.109 mg selenium/L urine) were higher than the average urine selenium levels of preemployment applicants (average, 0.034 mg selenium/L urine; range, 0–0.15 mg selenium/L). Garlic

breath, skin rashes, indigestion, lassitude, and irritability were noted, but no increase in mortality among exposed workers was detected. Smith and Westfall (1937) examined urine selenium levels in rural populations in Wyoming, South Dakota, and Nebraska and reported evidence of skin discoloration and lesions, tooth decay, diseased nails, gastrointestinal disturbances, and arthritis in individuals with urine selenium levels of 0.2–1.98 mg selenium/L; however, the authors did not show a significant correlation between clinical signs and the level of selenium in the urine. Longnecker et al. (1991) examined ranchers in the same area of the United States where selenosis of livestock had been observed. No clinical effects were observed with concentrations up to 2.2 mg/L in urine. Yang et al. (1983, 1989a, 1989b) measured mean blood, urine, and hair selenium levels of 3.2 mg selenium/L, 2.68 mg selenium/L, and 32.2 µg selenium/g, respectively, in a high selenium area where chronic selenosis was common in China. The clinical signs of selenium intoxication included loss of hair and nails, skin lesions, tooth decay, and nervous system disorders. In another area of China with high environmental levels of selenium but no signs of chronic selenosis in the population, blood selenium levels averaged 0.44 mg selenium/L (with a range from 0.35 to 0.58 mg selenium/L).

At blood levels of from 0.06 to 0.20 mg selenium/L, Deguchi (1985) found selenium to be positively correlated with grasping power and blood pressure in normal men and women and with hematocrit and hemoglobin concentrations in normal women. Similar correlations were not found in subjects with proteinuria or hypertension. In addition, Gebre-Medhin et al. (1988) found that in healthy children, serum selenium levels of 0.055–0.082 mg selenium/L were positively correlated with serum cholesterol, serum triglycerides, low and very low density lipoproteins, and apolipoproteins. Similar correlations were not found in diabetic children, who have slightly elevated serum selenium levels.

Biomarkers of Deficiency. Two endemic diseases, Keshan disease and Kashin-Beck disease, have been reported in selenium-deficient populations in China in which mean hair, blood, and urine selenium levels are low (Yang et al. 1988). Keshan disease, manifested as nausea, vomiting of yellowish fluid, and necrosis of the myocardium, has been found in a population with an average whole blood selenium concentration of 0.018 mg selenium/L, an average urinary concentration of 0.007 mg selenium/L, and an average hair selenium concentration of 0.123 µg/g (Yang et al. 1988). Kashin-Beck disease, which causes atrophy, degeneration, and necrosis of cartilage tissue, was observed in selenium-deficient areas in China in which the average selenium concentration in hair ranged from 0.077 to 0.165 µg selenium/g and blood selenium concentrations averaged approximately 0.02 mg selenium/L. In nonaffected areas in China, the selenium content in hair is greater than 0.2 µg selenium/g and in blood is greater than 0.06 mg selenium/L (Yang et al. 1988). These selenium-deficiency diseases are unlikely to occur in persons in the

United States. If selenium is not added to parenteral nutrition solutions, persons on long-term total parenteral nutrition are at risk for developing selenium deficiency symptoms which include cardiomyopathies, muscle pain, and weakness (Thomson 1991).

There is also some evidence that low serum selenium levels are associated with increased cancer risk, but this is not conclusive (Hojo 1981a; Willett et al. 1983). Salonen et al. (1984) concluded that an increased risk of cancer (a combination of gastrointestinal, respiratory, urogenital, hematologic, dermal, and skeletal cancers) in humans in Finland is associated with serum selenium levels of 0.045 mg selenium/L and below. Virtamo et al. (1987) found that cancer patients in Finland, including individuals with gastrointestinal, respiratory, skin, skeletal, urogenital, and hematological cancers, had slightly but not significantly lower serum selenium levels (mean and standard error of 0.0539±0.0015 mg selenium/L) compared with noncancer patients (0.0553±0.0005 mg selenium/L). However, serum selenium is generally an indicator only of very recent selenium status. As such, serum selenium may indicate an effect of cancer (malabsorption or anorexia) rather than a cause (Lockitch 1989; van't Veer et al. 1990).

A deficiency of selenium is also associated with cardiomyopathy (Johnson et al. 1981; Oster et al. 1983). Salonen et al. (1982) noted a statistically significant association between serum selenium concentrations of less than 0.045 mg selenium/L and the adjusted relative risk of coronary death, cardiovascular death, and myocardial infarction. Hojo (1981a) noted that patients with epilepsy had significantly lower urinary selenium levels than controls.

3.8.2 Biomarkers Used to Characterize Effects Caused by Selenium

Specific biomarkers of selenium effects were not found. Garlic breath is a marker of over-exposure to selenium compounds. However, as other metals that are methylated (e.g., arsenic) also result in garlic odor of the breath, this effect is not a unique marker of selenium over-exposure. Hair and nail effects may be the most frequent effects of overexposure to selenium. Hair becomes dry and brittle and breaks off at the scalp. Nails are also brittle and have white spots and longitudinal streaks, and break off easily (Lockitch 1989). Although these effects may not be specific to selenium, if they are observed, a determination of selenium status may be useful.

Yang et al. (1989b) have used increased prothrombin time (increased clotting time), a measure of hepatic damage, as a biomarker for selenium but their interpretation of their observations may be unwarranted. The difference they saw in affected humans was very small (1 second); prothrombin time has not been

previously demonstrated to correlate with symptoms of selenosis nor used to detect selenosis; finally, since the test has not been widely used, the results reported for the small number of affected individuals may be within the range of normal values for the general population or a subpopulation (IRIS 1996).

In humans and in animal studies, high concentrations of selenium have been demonstrated to cause neurological effects. Biomarkers of effect for the neurological system have been reviewed by ATSDR (OTA 1990).

3.9 INTERACTIONS WITH OTHER CHEMICALS

A wide variety of interactions of selenium with essential and nonessential elements, vitamins, xenobiotics, and sulfur-containing amino acids have been demonstrated in numerous studies. Selenium has been reported to reduce the toxicity of many metals including mercury, cadmium, lead, silver, and to some extent, copper (Frost 1972). Most forms of selenium and arsenic interact to reduce the toxicity of both elements (Levander 1977). Because of selenium's role in the antioxidant glutathione peroxidase enzymes, selenium also reduces the toxicity of metals in vitamin E–deficient animals (Diplock et al. 1967).

The interactions of selenium with other elements and compounds are complex and not well understood (Naganuma et al. 1983; NAS 1976a). The degree to which selenium is toxic, is taken up by tissues, or is excreted can be influenced by these interactions. Some of the major interactions of selenium compounds with other elements and compounds are described below.

Arsenic. In general, arsenic antagonizes selenium toxicity (Levander 1977). This effect extends to selenium in sodium selenite and selenate, seleniferous wheat, selenocystine, and selenomethionine (Levander 1977). However, a very pronounced synergistic toxicity exists between arsenic and two methylated selenium metabolites, trimethylselenonium ion and dimethyl selenide (Obermeyer et al. 1971). One of the more striking demonstrations is the antagonism of arsenic-induced terata in rodents by concomitant selenium exposure (Holmberg and Ferm 1969), and pretreatment of mice with sodium selenite reduced the clastogenic effects of a subsequent dose of sodium arsenite (Biswas et al. 1999b). Moxon et al. (1945) found that arsenic could reduce selenium toxicity when compounds of both elements were injected subcutaneously, thereby indicating that arsenic did more than interfere with the gastrointestinal absorption of selenium. Kamstra and Bonhorst (1953) found that arsenic reduced the excretion of volatile selenium compounds in expired air following the injection of compounds of both

elements into rats at acutely toxic levels. Levander and Baumann (1966a) found that the amount of selenium retained in the liver decreased and the amount of selenium appearing in the gastrointestinal tract increased as the dose of administered arsenic was increased. Experiments with rats and guinea pigs with cannulated bile ducts confirmed that arsenic increased the biliary excretion of selenium and that selenium increased the biliary excretion of arsenic (Levander and Baumann 1966b). It has recently been suggested that the mutual reduction in toxicity of arsenic and selenium administered together is due to the formation of an arsenic-selenium compound, seleno-bis(S-glutathionyl)arsinium (Gailer et al. 2000b). This compound was isolated from the bile of rabbits injected with selenium and arsenic and identified by X-ray spectroscopy.

Cadmium. Selenium can antagonize the nephrotoxic and hepatotoxic effects of cadmium in rats (Flora et al. 1982; Lindh et al. 1996; Nehru and Bansal 1996; Stajn et al. 1997), the inflammation, atrophy, and necrosis induced by cadmium in testes of rats (Jones et al. 1997; Mason and Young 1967; Ohta and Imamiya 1986; Wlodarczyk et al. 1995; Yiin et al. 1999), and the cardiotoxicity of cadmium in rats (Jamall et al. 1989). The protective effects are thought to occur as a result of the formation of a selenium-cadmium complex of high molecular weight (Chen et al. 1975; Jamall et al. 1989; Jamba et al. 1997; Ohta and Imamiya 1986).

Fluoride. Fluoride ion may interact with selenium; however, the degree and types of interaction depend upon the chemical form of selenium (i.e., organic or inorganic) and the dose. Moxon and DuBois (1939) reported that fluoride increased the toxicity of selenium in rats at 5 mg fluoride/L in the drinking water of young rats fed a diet containing 11 ppm selenium (0.55 mg selenium/kg/day) as seleniferous wheat. Selenium decreased growth and increased mortality in rats drinking fluoridated water compared to rats drinking deionized water. These results were disputed by Hadjimarkos (1969a) who administered 3 mg selenium/L as sodium selenite (0.15 mg selenium/kg/day) either with or without 50 mg fluoride/L as sodium fluoride in the drinking water of rats. The growth and mortality data indicated that the combined administration of selenium and fluoride under the conditions used did not increase selenium toxicity. However, the amount of administered fluoride was significantly higher and the amount of administered selenium significantly lower in the Hadjimarkos (1969a) study than the amounts administered by Moxon and DuBois (1939). No additional studies were located that reexamined the possible interaction between fluoride and selenium.

Iodine. Iodine and selenium interact to affect thyroid function. There are at least two aspects to this interaction. First, selenium is an important component of the iodothyronine 5'-deiodinases which

functions in the control of circulating triiodothyronine. Second, during the production of the thyroid hormone, hydrogen peroxide is produced, which is detoxified by GSH-Px. One possible consequence of the interaction between iodine and selenium has been noted in human populations deficient in iodine. In some iodine-deficient regions, a reversible hypothyroidism with goiter formation is observed. In other iodine-deficient areas, hypothyroidism is accompanied by thyroid gland destruction. The thyroid gland destruction is thought to result in populations that are deficient in both iodine and selenium (Contempré et al. 1991a, 1992, 1995). This hypothesis has been supported by a study in rats which found that iodine and selenium deficiency increased necrosis and induced fibrosis in the thyroid gland. Supplementation with iodine in selenium-deficient rats resulted in greater toxicity, possibly as a result of hydrogen peroxide which could not be detoxified because of the lack of GSH-Px (Contempré et al. 1995). This study suggests that iodine supplements may produce adverse effects in selenium-deficient individuals.

Mercury. Simultaneous administration of mercury and selenium in equimolar doses to animals resulted in decreased toxicity of both elements in acute and chronic studies with inorganic and organic mercury and with either inorganic or organic selenium compounds, although inorganic forms of selenium appear to be more effective than organic forms (Chang 1983; Rao et al. 1998; Skerfving 1978). Selenium protects against the acute nephrotoxicity of the mercuric ion and methylmercuric ion in rats (Ganther et al. 1972; Hansen 1988; Magos et al. 1987; Parizek and Ostadalova 1967) and possibly against acute neurotoxicity of the methylmercuric ion in rats (Ohi et al. 1980). The protective effect of selenium has been associated with a higher whole body retention of mercury rather than with increased mercury excretion (Hansen 1988; Magos et al. 1987). Selenium has been shown to inhibit biliary excretion of methyl mercury in rats (Urano et al. 1997), while mercury exposure reduces urinary selenium excretion in humans (Ellingsen et al. 1995). Although the mechanism of the interaction has not yet been elucidated, selenium and mercury appear to form a metabolically inert compound by reaction with GSH (Gailer et al. 2000b). Further support for the role of this compound comes from the observation that selenium-treated animals can remain unaffected despite an accumulation of mercury in tissues to levels that are otherwise associated with toxicity (Skerfving 1978). Additional support comes from the 1:1 ratio of selenium and mercury found in the livers of marine mammals and in the bodies of experimental animals injected with mercury and selenium, regardless of the ratio of the administered doses (Hansen 1988).

Although the fetotoxicity of methylmercuric chloride has been enhanced in selenium-deficient mice (Nishikido et al. 1987), additional selenium administration does not appear to protect against teratogenic effects (i.e., cleft palate) of methylmercuric chloride in mice (Lee et al. 1979). High doses of selenium administered as selenite for 30 days prior to gestation and through gestation day 18 to mice fed a diet

containing high doses of methylmercuric chloride increased the incidence of cleft palate (Nobunaga et al. 1979). Concurrent treatment of pregnant or lactating mice receiving nontoxic doses of methyl mercury in drinking water with selenomethionine increased the deposition of mercury in the offspring (Nielsen and Andersen 1995).

Methionine and Vitamin E. Combinations of methionine and vitamin E have been found to be antagonistic to selenium toxicity. In one study, selenium concentrations in the liver and kidneys of rats fed selenium-containing diets with methionine and vitamin E were less than the concentrations found in the livers and kidneys of rats fed selenium with either methionine or vitamin E alone (Levander and Morris 1970). The results are compatible with the hypothesis that methionine detoxifies selenium by forming methylated derivatives of selenium that are eliminated in the urine and in expired air (see Section 3.4.4) or that methionine and selenomethionine are in the same pool of amino acids and that by increasing the amount of methionine relative to selenomethionine, the probability of selenomethionine being randomly inserted into proteins during synthesis decreases (Stadtman 1977, 1980, 1983, 1987, 1990). As discussed in Section 3.11, methionine administered as an antidote for acute selenium toxicity in rats was ineffective (Lombeck et al. 1987). This result supports a mechanism of action involving protein synthesis rather than a methylation mechanism hypothesis.

Silver. Selenium has been shown to be protective against the hepatotoxic effects of silver in vitamin E–deficient rats. A 0.15% solution of silver acetate in the drinking water of rats produced necrotic degeneration of the liver and high mortality. Dietary selenium supplementation at 1 mg selenium/kg food resulted in a significant reduction in the toxic effects of silver (Diplock et al. 1967). One report indicates a nontoxic dose of silver acetate in rats minimizes effects of acute selenium toxicity. However, the body burden of selenium in several organs increased with treatment with silver acetate. It is postulated that this antagonistic effect may be due to the formation and disposition of silver selenides which are relatively insoluble and nontoxic (Eybl et al. 1992).

Sulfate. Sulfate appears to reduce the growth inhibition that results from dietary exposure of rats to high levels of selenite or selenate (Halverson and Monty 1960). Sulfate does not appear to be protective against selenium-induced liver damage (Halverson and Monty 1960).

Antagonistic interactions with several additional metals including antimony, germanium, and bismuth have been reported (Paul et al. 1989). Complex interactions of selenium with other metals, vitamins, and nutrients usually lead to a reduced toxicity of selenium and/or a reduced toxicity of the interacting

substance. However, vitamin C (ascorbic acid) may increase the absorption and toxic effects of selenium in humans (HSDB 2001; Lombeck et al. 1987; Mack 1990; Martin et al. 1989a, 1989b). The relevance of these interactions to selenium exposure of the general public is unknown. Many review articles are available concerning the interactions of selenium and other chemicals, including those by Combs, Jr., and Combs (1987), Hansen (1988), Levander and Morris (1970), Magos and Webb (1980), Naganuma et al. (1983), and Whanger (1981).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to selenium than will most persons exposed to the same level of selenium in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of selenium, or compromised function of organs affected by selenium. Populations who are at greater risk due to their unusually high exposure to selenium are discussed in Section 6.7, Populations With Potentially High Exposures.

Data concerning human subpopulations with unusual susceptibility to the toxic effects of selenium were not located. Epidemiologic studies have identified populations with very low or very high nutritional status, and these groups are expected to have very different responses to selenium exposures. Pregnant and nursing women are believed to require more selenium than the general public (NRC 1989).

It is possible that persons exposed to high fluoride levels in drinking water might be at greater risk of adverse health effects from exposure to excessive levels of selenium (Moxon and DuBois 1939; Yang et al. 1989a), but evidence on this point is equivocal (Hadjimarkos 1969a) and requires further study. Individuals with vitamin E–deficient diets might also be at greater risk of liver damage from exposure to excess selenium (Levander and Morris 1970). Based on studies of chemically induced diabetes in rats, selenium may change insulin needs (McNeil et al. 1991). Therefore, insulin-dependent diabetics may be more sensitive to adverse health effects due to selenium exposure than the general population.

Cretins or other individuals with iodine or thyroid deficiencies may be more sensitive to adverse health effects from selenium exposure (Contempré et al. 1991b, 1992). Iodine supplementation of these individuals without selenium supplementation may further exacerbate the effects. The elderly may be less susceptible to the negative effects of selenium and more prone to selenium deficiencies. A number of

researchers have reported lower absorption of selenium and lower selenium tissue concentrations in the elderly compared to younger adults (Martin et al. 1991; Morisi et al. 1989).

Populations living in the western United States in areas eating produce grown in highly seleniferous soils could be at greater risk of adverse health effects from additional environmental exposure to selenium if their selenium nutritional status is already high (see Section 6.6).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to selenium. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to selenium. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to selenium:

Nadig RJ. 1994. Cadmium and other metals and metalloids. In: Goldfrank LR, Weisman RS, Flomenbaum N, et al. eds. Goldfrank's toxicological emergencies. 6th ed. Norwalk, CT: Appleton and Lange, 1342-1343.

Mofenson HC, and Caraccio TR. 1998. Toxicity of household products. In: Viccellio P, ed. Emergency toxicology. 2nd ed. Philadelphia, PA: Lippincott-Raven, 519.

3.11.1 Reducing Peak Absorption Following Exposure

No specific recommendations have been reported for reducing absorption following acute high-dose exposure to selenium or selenium compounds via inhalation or dermal exposure (Gosselin et al. 1984; HSDB 2001). There have been very few reported cases of overexposure via inhalation in industrial settings but some have resulted in toxic effects (Lockitch 1989). General procedures suggested for reducing absorption following accidental industrial exposure include moving the exposed person into fresh air, removing contaminated clothing and shoes, and flushing exposed skin or eyes with running water (HSDB 2001).

Oral exposures to toxic quantities of selenious acid, sodium selenate, and selenium dioxide have been reported (Lockitch 1989). In general, only supportive treatment has been recommended (HSDB 2001; Mack 1990). In some cases, gastric lavage and induction of vomiting by use of emetics have been

reported to be useful in reducing absorption, but because selenious acid (in gun blueing, pH 1) is caustic, both procedures could result in additional damage by this compound (Lombeck et al. 1987; Mack 1990). The possibility of a sudden onset of shock, seizures, severe hypotension, and cardiorespiratory arrest has been used to argue against emesis (Mack 1990). It has also been suggested that oils and alcohol are to be avoided in treatment of ingested selenium sulfide because these agents may increase absorption (Gosselin et al. 1984).

3.11.2 Reducing Body Burden

In acute exposure situations, selenium compounds are rapidly absorbed and widely distributed throughout many organ systems following inhalation or ingestion (see Section 3.4.2). Extensive parenteral fluid administration has been used to force the urinary excretion of selenium (Lombeck et al. 1987). Chelating agents have not been effective in experiments, and both calcium disodium ethylene diamine tetraacetate (EDTA) and dimercaprol (British Anti-Lewisite, BAL) may increase the toxic effects of selenium (Lombeck et al. 1987; Mack 1990; Paul et al. 1989). Although vitamin C (ascorbic acid) is used to reduce the body burdens of other metals, it may also increase the absorption and toxic effects of selenium in humans (HSDB 2001; Lombeck et al. 1987; Mack 1990; Martin et al. 1989a, 1989b). Bromobenzene has been reported to increase the urinary excretion of selenium, but because bromobenzene is also a hepatic toxin, its use is dangerous (Gosselin et al. 1984; HSDB 2001).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The exact molecular mechanism of toxic action by selenium and selenium compounds is not known. One theory is that at a biochemical level, selenium inactivates sulfhydryl enzymes leading to depression of cellular oxidative processes (Lombeck et al. 1987; Mack 1990; Shamberger 1981). No information was located on established therapies designed to interfere with this possible mechanism of action of selenium. Because selenomethionine is known to randomly insert into proteins, rats were treated with methionine after acute selenosis had developed, but no effect was observed (Lombeck et al. 1987). However, pretreating rats with dietary methionine and vitamin E reduced the toxicity of dietary selenium as measured by decreased liver damage, reduced body weight gain, and decreased liver and kidney concentrations of selenium compared to those in rats that had not received supplements (Levander and Morris 1970). Inorganic sulfate fed simultaneously with selenite or selenate in the diet protected rats from the toxicity of selenium as measured by body weight gain; however, sulfate did not protect against

liver necrosis caused by selenium (Halverson et al. 1962). It would, therefore, seem plausible that another nontoxic sulfur-containing chemical could be found to be effective against acute selenium toxicity.

The search for an agent that both reduces the acute toxicity of selenium and increases the excretion of the selenium compound formed has proved difficult (Paul et al. 1989). In some experimental cases, other metals have been shown to mitigate the toxicity of selenium, possibly by forming metal selenides with low solubility and toxicity (see Section 3.9). Several metal-containing compounds were tested for efficacy in reducing toxic effects and increasing elimination of selenium from sodium selenate injected into rats. Germanium citrate is nontoxic and was found to be effective both at reducing toxic effects and increasing the rate of selenium elimination. However, the germanium compound, bis-carboxyethyl germanium sesquioxide, had no positive effect on toxicity or distribution to organs but did increase the amount of selenium excreted in the urine (Paul et al. 1989). In mice, pretreatment with a nontoxic dose of silver acetate was shown to reduce the toxic effects of sodium selenite. However, this treatment increased the whole body burden of selenium, and the concentrations in several organs were raised compared to those in the controls injected with sodium selenite only (Eybl et al. 1992).

3.12 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of selenium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of selenium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Selenium

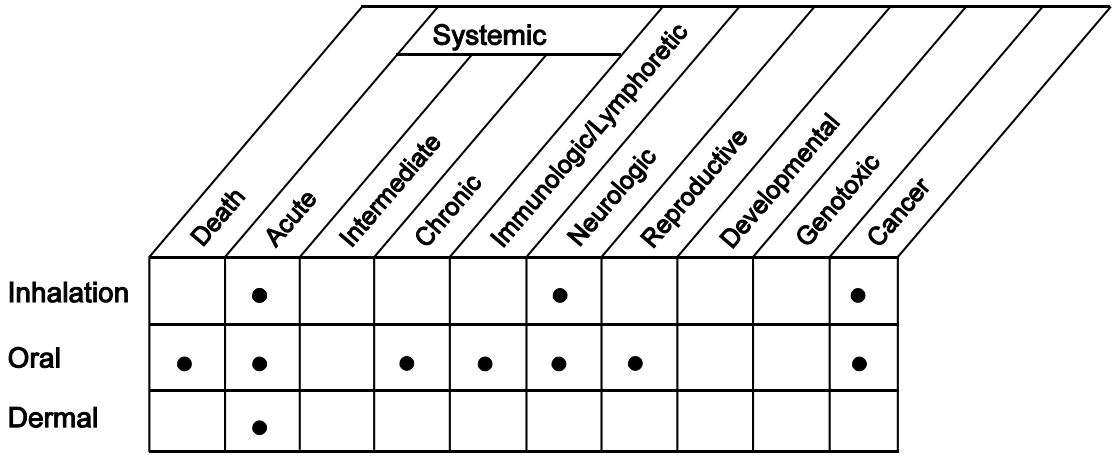
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to selenium are summarized in Figure 3-10. The purpose of this figure is to illustrate the existing information concerning the health effects of selenium. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As seen in Figure 3-10, very little quantitative information is available regarding the health effects in humans exposed to selenium compounds via inhalation. The only quantitative inhalation studies in humans that relate selenium exposure levels or selenium body levels to health effects following inhalation exposure are epidemiological cancer studies. Fatalities following inhalation exposure to selenium compounds have not been reported. Despite the large number of cases of reported inhalation exposures in occupational settings, characterization of exposure concentrations and the selenium compounds present in the air are generally lacking. It is therefore not possible to link the degree and types of symptoms reported in workers to selenium exposure levels. There have been no reports of immunological, developmental, reproductive, or genetic effects in humans resulting from inhalation exposure to selenium compounds. Complaints of dizziness and fatigue have accompanied occupational inhalation exposures, but characterization of the exposure levels required to produce neurological symptoms is lacking.

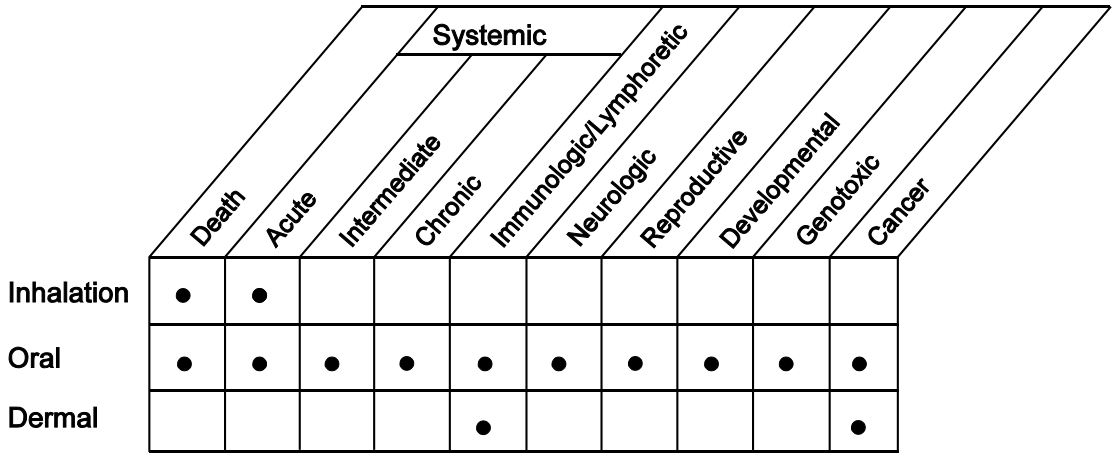
Most of the information concerning the health effects in humans following exposure to selenium and selenium compounds is for the oral exposure route. However, exposure levels associated with the few documented fatalities resulting from accidental or suicidal poisoning with selenium compounds are lacking, as are exposure levels for other nonfatal poisonings by ingestion. A series of epidemiological studies in China have provided the only data about chronic exposure levels to excess dietary selenium that resulted in adverse effects on skin, nails, and hair and in possible neurological effects.

Older reports from the western United States described similar symptomology in the 1930s but did not characterize daily selenium intake. More recent reports show no clinical symptoms in the same area. The

Figure 3-10. Existing Information on Health Effects of Selenium



Human



Animal

● Existing Studies

possible inverse relationship between dietary selenium intake and the risk of various types of cancer has been examined in numerous epidemiological studies in the United States and in other countries.

Concern for the dermal route of exposure to selenium compounds as a cause of adverse health effects in humans is extremely low except for the acid forms, which owe their dermal effects to their acidity more than to their selenium content. Selenium sulfide, an ingredient in some antidandruff shampoos, does not appear to be absorbed through the skin. Ingestion of large amounts of the compound, however, would be of concern because selenium sulfide has been shown to be carcinogenic in rats and mice following oral exposure.

Data are available for acute inhalation exposures for a few of the volatile selenium compounds that have resulted in the death of animals. These exposures also produced signs of central nervous system toxicity, lung injury, and possible damage to heart and liver. No studies were located concerning health effects in animals following intermediate or chronic inhalation exposures to volatile selenium compounds or selenium dust.

In animals, the focus on the oral toxicity of selenium has taken two routes, one in laboratory animals and the other in studies of selenium toxicity to livestock. In laboratory animals, attention has been directed toward the hepatotoxic properties of selenites, selenates, and selenium contained in grains following early reports that selenium produced hepatic carcinomas in rats. An intermediate-duration study has also shown that selenate and selenite can cause kidney effects in rats while mice are less sensitive to this effect of selenium compounds. In recent years, much of the research in laboratory animals using the oral route of administration of selenium compounds has been directed toward the anticarcinogenic properties of selenium compounds.

In livestock, concern for selenium toxicity and deficiency is high. In areas of the country with selenium-poor soils, dietary selenium supplementation for livestock has been necessary to prevent chronic selenium deficiency diseases. Dietary supplementation programs have resulted in cases of accidental poisonings from misuse of the selenium supplements (Hopper et al. 1985).

3.12.2 Identification of Data Needs

Acute-Duration Exposure. The primary target organ in humans following acute exposure to high concentrations of selenium by inhalation or oral routes is the lung, with cardiovascular, hepatic, and renal systems all affected (lesser systemic effects were observed in all other organ systems except the musculoskeletal system) (Carter 1966; Civil and McDonald 1978; Clinton 1947; Koppel et al. 1986; Wilson 1962). Two case reports of acute dermal exposure were also located; the results revealed effects on the skin and eyes (Middleton 1947; Pringle 1942). Additional epidemiological or occupational studies would be useful to further characterize the effects of acute exposure via all routes and to confirm the target organ data.

Studies regarding single inhalation or oral exposures of rats, guinea pigs, rabbits, and mice have provided information on lethal levels of exposure to selenium compounds (Cummins and Kimura 1971; Dudley and Miller 1941; Hall et al. 1951; Miller and Williams 1940; Olson 1986; Smyth et al. 1990). However, few levels at which sublethal effects first appear have been identified. Clinical observations and gross necropsies have been performed, but no single-dose exposure study has included internal examination of the animals to identify dose-response data for sublethal systemic toxic effects. Such studies might provide information on the thresholds for systemic toxicity following single-dose exposure. Repeated inhalation exposure studies in animals are limited to a few days of exposure (Hall et al. 1951). Although the studies have demonstrated cumulative toxicity following repeated inhalation exposure to inorganic selenium compounds, effects other than lethality have been poorly characterized. Single-dose exposure studies have been conducted with selenium monosulfide in mice (target systems: respiratory and neurological) and selenium disulfide in rats (target organ not specified); however, the results have varied and there is uncertainty about which or how much of each of the compounds was administered. There were no effects in mice following acute dermal exposure. Additional dermal exposure studies in animals would be useful to confirm the effects found in humans. The data were insufficient for the derivation of acute oral and inhalation MRLs.

Intermediate-Duration Exposure. No human studies of intermediate inhalation exposure to selenium were located. Following oral exposure, one study in humans revealed endocrine effects in iodine-deficient individuals (Contempré et al. 1991a, 1992) and others revealed endocrine effects in individuals receiving sufficient levels of iodine (Duffield et al. 1999; Hawkes and Keim 1995). Results from one study in humans revealed dermal effects following intermediate dermal exposure (Pringle

1942). There were insufficient data to derive intermediate MRLs. Additional epidemiological or occupational studies would be useful in elucidating the potential target organs and effect levels.

No intermediate inhalation studies were located in animals. Intermediate-duration inhalation studies, in which selenium is administered as selenium dioxide, hydrogen selenide, or selenium dust, might help to identify air concentrations of these substances that produce sublethal effects not only on the respiratory system, but also on the hepatic, renal, hematological, and cardiovascular systems. As exposure to the selenoamino acids is via ingestion, inhalation studies of these compounds would not be necessary.

Intermediate-duration oral exposure studies have been performed with rats, pigs, mice, and monkeys at several dose levels using several selenium compounds (Baker et al. 1989; Behne et al. 1992; Bioulac-Sage et al. 1992; Chen et al. 1993; Cukierski et al. 1989; Das et al. 1989b; Eder et al. 1995; Halverson et al. 1966; Hasgawa et al. 1994; Hotz et al. 1997; Mahan and Magee 1991; Mihailovic et al. 1992; NTP 1980c, 1994; Palmer and Olson 1974; Panter et al. 1996). The major effects were hepatic, dermal, endocrine and neurological. Additional studies are needed to confirm these data. No intermediate-duration dermal administration studies have been conducted with the environmental forms of inorganic selenium likely to be of concern (e.g., sodium selenate and sodium selenite), although it is unlikely that these forms would be dermally absorbed to a significant degree. Dermal application of selenomethionine to the skin of mice did not result in any direct effects on the skin, or other signs of toxicity, although it was absorbed (Burke et al. 1992b). The organic compounds of selenium are usually not free in the environment but, rather, contained in plant and animal material. Therefore, no further dermal studies would be useful.

Chronic-Duration Exposure and Cancer. Several occupational studies of chronic inhalation exposure to inorganic selenium compounds were located (Glover 1967; Holness et al. 1989; Kinnigkeit 1962). Effects reported in these studies were primarily respiratory, although cardiovascular, gastrointestinal, hematological, musculoskeletal, dermal, ocular, and neurological effects were also noted. Animal data are not available for inhalation exposures of chronic duration. Data in this area would be helpful to establish an animal model for respiratory effects of inorganic selenium compounds, since most human exposure has been occupational and to a variety of compounds. Neurological effects have been documented in animals after chronic oral exposure, but further study of neurological effects in animals after inhalation exposure is needed to provide a model for the effects observed after occupational exposure in humans. Following chronic oral exposure, the primary effects in humans were dermal, neurological and endocrine (Brätter and Negretti De Brätter 1996; Clausen et al. 1989; Longnecker et al.

1991; Yang et al. 1983, 1989a, 1989b; Yang and Zhou 1994). An MRL has been derived for chronic oral exposure to selenium based on a NOAEL for dermal effects. One case report of chronic dermal exposure revealed dermal effects (Senff et al. 1988). Additional epidemiological or retrospective studies of chronic exposure would be helpful for confirming the existing data. Studies examining the role of nutrition in selenium toxicity would be especially useful.

Although the lung does not appear to be a target organ in animals after chronic oral exposure to selenium compounds, data have not been adequately reported (Harr et al. 1967; Henschler and Kerschner 1969; Schroeder and Mitchener 1972), and further studies might be useful to fully rule out these effects. Studies examining possible gastrointestinal and musculoskeletal effects in animals after chronic exposure to selenium or selenium compounds or to seleniferous grains might be helpful in determining the mechanisms of alkali disease whose symptoms have been observed in grazing livestock (Harr et al. 1967; Shamberger 1986). Hepatic and renal lesions following chronic selenium exposure have been adequately characterized. Investigations of systemic effects associated with chronic oral administration of selenium compounds, however, have been limited.

No studies were located regarding carcinogenic effects in animals after chronic inhalation exposure to selenium or selenium compounds. No further investigation is needed since humans have not been shown to have an increased risk of malignancy from selenium exposure. The majority of oral studies have provided information on the absence of carcinogenic effects in humans and animals (Beems 1986; Clark et al. 1996a, 1999; Coates et al. 1988; Harr et al. 1967; Menkes et al. 1986; Thompson and Becci 1979; Virtamo et al. 1987). However, earlier and less complete studies had suggested that selenium was carcinogenic following oral exposure of animals (Nelson et al. 1943; Schroeder and Mitchener 1971a; Volgarev and Tscherkes 1967). Chronic oral exposure studies conducted in mice and rats by gavage administration of a mixture of selenium monosulfide and selenium disulfide produced liver tumors in rats and lung tumors in female mice (NTP 1980c). The relative proportion of the two compounds was not clear, although physical evidence suggested that the dose solution was primarily selenium monosulfide. Further studies utilizing selenium sulfides might be useful in determining possible effects in humans.

Genotoxicity. Chromosomal aberrations and sister chromatid exchanges in lymphocytes were not increased in humans treated (oral or intramuscular injection) with sodium selenite (Norppa et al. 1980a). Compared to untreated controls, a significant increase in the number of micronuclei was observed in bone marrow cells of mice treated orally with selenite or selenate, and macaques treated orally with L-selenomethionine (Biswas et al. 1997, 1999a; Choy et al. 1989; Itoh and Shimada 1996; Rusov et al.

1996). A significant increase in the number of micronuclei in bone marrow cells was not observed in the offspring of macaques treated with L-selenomethionine on gestation days 20–50 (Choy et al. 1993).

Genotoxicity studies (*Salmonella*/microsome assays, sister chromatid exchange, and tests of unscheduled DNA synthesis and of chromosome aberrations in cultured mammalian cells) indicate that selenite, selenate, and selenide have both genotoxic and antigenotoxic effects (Biswas et al. 1997, 2000; Gairola and Chow 1982; Khalil 1994; Lu et al. 1995b; Schillaci et al. 1982; Ueda et al. 1997; van der Lelie et al. 1997). The underlying mechanisms responsible for the varying genotoxicity results remain to be elucidated.

Reproductive Toxicity. One study that measured the concentration of selenium in sperm samples indicated no correlation between selenium concentrations and sperm count or motility (Roy et al. 1990). No significant increase in spontaneous abortions was reported among women chronically exposed to drinking water containing 7–9 µg selenium (Vinceti et al. 2000a). No other human studies were located. A few reproductive toxicity studies in animals (Chowdhury and Venkatakrishna-Bhatt 1983; Harr and Muth 1972; NTP 1996; Schroeder and Mitchener 1971b; Wahlstrom and Olson 1959b) indicate that oral exposure to excess sodium selenite can reduce female fertility, although male fertility appears not to be affected. Oral treatment of rats with sodium selenate or selenite has been shown to increase the number of abnormal sperm in males (El-Zarkouny et al. 1999; Kaur and Parshad 1994; NTP 1994), produce testicular hypertrophy (Turan et al. 1999a), and affect the estrous cycle (NTP 1994, 1996). Fertility was not examined in these studies. Selenium dioxide produced testicular degeneration following intraperitoneal administration to rats (Chowdhury and Venkatakrishna-Bhatt 1983). Disturbances in the menstrual cycle (anovulation, short luteal and follicular phases) were observed in monkeys treated orally with L-selenomethionine (Cukierski et al. 1989) and mice treated orally with sodium selenite (Nobunaga et al. 1979). Studies of both male and female reproductive toxicity of selenium following oral and inhalation exposure in rats and other mammals to selenium dioxide and other forms of selenium, both organic and inorganic, would be useful. Such studies could provide information regarding the reproductive effects of the various forms of selenium that might be encountered in occupational settings, at waste sites, and in the drinking water and food from highly seleniferous areas of the United States.

Developmental Toxicity. No developmental studies were found regarding inhalation or dermal exposure in humans or animals. Developmental studies using the oral route of administration indicate that excessive sodium selenate or sodium selenite intake can result in fetal toxicity and reduced growth in experimental mammals (Dinkel et al. 1963; Ferm et al. 1990; NTP 1996; Rosenfeld and Beath 1964;

Wahlstrom and Olson 1959a), but generally only at doses that produce maternal toxicity. Developmental effects were not observed in macaque fetuses from mothers given toxic oral doses of L-selenomethionine during gestation (Tarantal et al. 1991). Intravenous injection of sodium selenite in mice did not indicate that the compound is teratogenic in rodents (Yonemoto et al. 1984). Intravenous injections of sodium selenate, D,L-selenomethionine, and D,L-selenocystine into neonatal rats indicated that some selenium compounds can contribute to the formation of one type of cataracts (Ostadalova and Babicky 1980). Cataracts were not observed in the offspring of macaques treated orally with L-selenomethionine during gestation (Tarantal et al. 1991). Additional developmental toxicity studies of selenium compounds in mammals do not seem to be necessary at this time.

Immunotoxicity. No studies were located regarding adverse immunological effects in humans following inhalation or oral exposure. One case report describes immunological effects following dermal exposure (Senff et al. 1988). Animal studies of possible adverse immunological effects from excessive exposure to selenium compounds are limited (Dudley and Miller 1941; Glenn et al. 1964a; Hall et al. 1951; Smyth et al. 1990). One study (Koller et al. 1986) included a battery of immunological tests, some of which indicated beneficial effects of sodium selenite administration and others that indicated adverse effects. Additional immunotoxicity tests, including challenges of the immune system, might characterize the significance of the different immunological effects that have been observed following selenium administration.

Other than selenium sulfide, an ingredient in some antidandruff shampoos, selenium compounds have not been tested for sensitization. The potential for dermal contact by humans does exist, however, in occupational settings and to a lesser extent in soil at waste sites.

Neurotoxicity. Data from an epidemiological study of humans and from studies in livestock indicate that the central nervous system is an end point of concern following oral exposure to selenium compounds (Baker et al. 1989; Boylan et al. 1990; Cukierski et al. 1989; Harrison et al. 1983; Panter et al. 1996; Rosenfeld and Beath 1964; Stowe et al. 1992; Tsunoda et al. 2000; Yang et al. 1983). Chronic oral exposure studies of laboratory animals that focus on behavioral effects and histopathological changes in the central nervous system might provide useful dose-response information on central nervous system effects.

Epidemiological and Human Dosimetry Studies. A few human epidemiological studies have identified blood selenium levels indicative of adequate selenium status and indicative of selenium toxicity. However, there are large differences in selenium blood levels in populations from different parts of the world (e.g., China, New Zealand, and Finland) (Salonen et al. 1985; Yang et al. 1989a). For example, blood selenium levels in healthy Finnish populations average 0.055 mg selenium/L (Virtamo et al. 1987), whereas blood selenium levels in healthy U.S. populations are much higher, averaging 0.206 mg selenium/L (Allaway et al. 1968). Extrapolation from the relationship between blood selenium levels and selenium toxicity in populations from one region of the world to populations in another region may not be appropriate. Studies examining the particular forms of selenium and the contribution of diet in determining individual and population selenium status would be useful. The selenium status of an individual will determine the magnitude of additional selenium intake that can be tolerated without resulting in adverse effects. Evidence for adverse effects on the endocrine system has also been found following intermediate and chronic oral exposure to elevated levels of dietary selenium in humans and animals (Brätter and Negretti De Brätter 1996; Behne et al. 1992; Eder et al. 1995; Hawkes and Keim 1995; Hotz et al. 1997). Studies of humans with high dietary intakes of selenium that monitored thyroid hormone levels and iodine intake would be useful. Studies of humans taking selenium supplements would also help further identify the long-term effects of selenium status on human health.

Biomarkers of Exposure and Effect.

Exposure. Selenium exposure can be correlated with concentrations detected in human blood, blood components, urine, hair, and nails. Selenium concentrations found in these biomarkers in the general population can be found in Table 3-7. However, these markers vary greatly among different populations (Longnecker et al. 1991). Levels of plasma, erythrocyte and platelet GSH-Px activity, as well as selenoprotein P may serve as better markers of selenium deficiency than selenium concentrations. Additional research into markers of selenium status in populations and how they may be used to estimate an additional selenium exposure that would be safe would be helpful.

Effect. Perhaps the earliest and most frequent symptoms of selenosis in humans are dry and brittle hair that breaks off, and brittle nails with white spots or streaks. Although these effects may not be specific to selenium, determination of selenium status may be useful if they are observed in a subject. Additional, biomarkers of negative effects that could be detected before clinical signs of selenium toxicity could be helpful in preventing selenium poisoning.

Absorption, Distribution, Metabolism, and Excretion. The absorption of selenium has been investigated in humans following oral exposure and in animals following oral and inhalation exposures (Finley 1998; Glover 1970; Griffiths et al. 1976; Martin et al. 1989a; Medinsky et al. 1981a; Sánchez-Ocampo et al. 1996; Thomson et al. 1977). In humans, no quantitative data exist on either the extent or rate of absorption of selenium from the lung or the skin. Information that selenium is absorbed following inhalation is limited to occupational case studies in which larger quantities of selenium have been measured in the urine of workers occupationally exposed to selenium. In order to understand all possible routes for human overexposure to selenium, information concerning the dermal and inhalation absorption of selenium and its compounds in humans would be useful, even though potential exposures to selenium might be more likely to occur by the oral route for the general public.

The oral absorption of different physical and chemical forms of selenium (e.g., selenite, selenate, and selenomethionine as solids or in aqueous solution) has been investigated in humans (Griffiths et al. 1976; Martin et al. 1989a; Moser-Veillon et al. 1992; Robinson et al. 1978; Swanson et al. 1991; Thomson 1974; Thomson and Stewart 1974; Thomson et al. 1977) and in animals (Finley 1998; Furchner et al. 1975; Thomson and Stewart 1973; Vendeland et al. 1992; Whanger et al. 1976). Oral absorption of naturally occurring selenium and the effects of dietary levels on the absorption of exogenous selenium have also been investigated (Young et al. 1982). These studies have revealed that several selenium compounds appear to be readily absorbed from the gastrointestinal tract of humans and animals. It also appears that the degree of absorption in humans is independent of the exposure level, but that in some cases, absorption is greater when a selenium deficiency exists.

Distribution studies in humans and animals indicate that selenium is widely distributed in the body and is concentrated in the liver and kidney following oral, intravenous, or subcutaneous exposures (Cavalieri et al. 1966; Finley 1998; Heinrich and Kelsey 1955; Jereb et al. 1975; Kaneko et al. 1999; Mahan and Kim 1996; Razagui and Haswell 1997; Shiobara et al. 1998; Thomson and Stewart 1973). Studies of intravenous administration of selenomethionine have indicated that animals and humans concentrate this compound in the pancreas, but it is unlikely that this selenium compound will be encountered in large quantities in the environment except in animals and plants along with other organic selenium compounds. It would be useful to know if selenomethionine concentrates in the pancreas of humans following oral intake. Following oral exposure, the distribution of selenium across the placenta into the fetuses of rats, hamsters, dogs, and monkeys (Archimbaud et al. 1992; Choy et al. 1993; Hawkes et al. 1994; Mahan and Kim 1996; Parizek et al. 1971a; Willhite et al. 1990) and the transfer of selenium from milk to suckling offspring of rats, dogs, and monkeys (Archimbaud et al. 1992; Choy et al. 1993; Hawkes et al. 1944;

Parizek et al. 1971a) have also been investigated. Selenium levels have been measured in human milk (Brätter and Negretti De Brätter 1996; Brätter et al. 1991b; Li et al. 1999; Michalke and Schramel 1998; Moser-Veillon et al. 1992; Rodríguez Rodríguez et al. 1999; Viitak et al. 1995; Yang 1989b) and the concentration of selenium in human milk has been shown to correlate with dietary intake (Brätter et al. 1991b). The uptake of selenium by erythrocytes and its subsequent metabolic alteration and ultimate binding to plasma proteins have been investigated (Sandholm 1973).

The metabolism of selenium is now fairly well understood. To become incorporated into selenium-specific proteins (e.g., glutathione peroxidase, thioredoxin reductase, iodothyronine 5'-deiodinase) through a cotranslational mechanism requires that selenium be in the form of selenide (Sunde 1990). All forms of selenium can be transformed to selenide, although the rates of transformation vary. For example, selenate is not converted to selenide as readily as selenite. The formation of selenide from selenocysteine requires a specific enzyme, selenocysteine β-lyase, which catalyzes the decomposition of selenocysteine to alanine and hydrogen selenide. Excess selenium is methylated and exhaled or excreted in the urine in both humans and animals. Further research is required to determine which selenium metabolites or intermediates lead to toxicity.

In humans and animals, intravenous and oral administration data indicate that the major route of selenium excretion is in the urine (Byard and Baumann 1967; Davidson-York et al. 1999; Finley 1998; Griffiths et al. 1976; Palmer et al. 1970; Patterson et al. 1989; Shiobara et al. 1998; Swanson et al. 1991). Excretion of selenium in feces constitutes a minor pathway immediately following exposure but the amount excreted can be equal to that excreted in urine depending on the chemical form of selenium administered, the size of the dose, and the length of time since dosing. Both human and animal studies indicate that the extent of excretion by any one route is related to the administered dose and the frequency of administration (Finley 1998; Lathrop et al. 1972; McConnell and Roth 1966; Shiobara et al. 1998; Thomson and Stewart 1974). The extent of excretion of selenium compounds in the expired air has been investigated in animals, but no quantitative studies in humans for this route exist; however, it is believed to be a minor pathway especially at lower doses (McConnell and Roth 1966; Olson et al. 1963).

Comparative Toxicokinetics. The target organs and adverse health effects are generally similar across species. However, the liver appears to be the primary target organ for the oral toxicity of selenium in animals following intermediate and chronic exposure (Baker et al. 1989; Biolac-Sage et al. 1992; Fitzhugh et al. 1944; Halverson et al. 1970; Harr et al. 1967; Hasegawa et al. 1994; Kolodziejczyk et al. 2000; Nelson et al. 1943; Palmer and Olson 1974; Sayato et al. 1993; Schroeder and Mitchener 1972;

Skowerski et al. 1997a; Turan et al. 1999a), whereas liver cirrhosis or dysfunction have not been found in reports of chronic selenosis in humans (Longnecker et al. 1991; Yang et al. 1989a). Different metabolites may help explain the cataract formation observed in neonatal rats and the teratogenic activity of selenium seen in birds but not in humans or other mammals (Tarantal et al. 1991). Toxicokinetic studies with some design similarities have been performed in humans and several animal species (Behne et al. 1991; Bopp et al. 1982; Cantor et al. 1975; Ganther 1979; Hawkes et al. 1992; Obemeyer et al. 1971; Palmer et al. 1970; Willhite et al. 1990, 1992). Comparative toxicokinetic studies, per se, have not been performed. PBPK models for selenium administered orally as selenite or selenomethionine have been developed for humans, but no animal models were located. Animal models for the oral route would be useful in assessing toxicokinetic similarities and differences between species.

Methods for Reducing Toxic Effects. Current methods for reducing toxic effects of selenium and selenium compounds after acute exposures are general supportive treatment methods based on those used for other toxic metals (HSDB 2001; Mack 1990). Although currently a rare form of poisoning, the use of selenious acid in gun blueing could make acute selenium exposure more common in households in the future. Additional research aimed at decreasing absorption, speeding excretion, and reducing the body burden of selenium would be valuable.

Children's Susceptibility. Limited information is available on the toxicity of selenium in children, but the available information suggests that children may be less susceptible to toxic effects of selenium than adults and more susceptible to deficiency. Most data comes from children living in areas of chronic high dietary selenium intake (Yang et al. 1989a, 1989b). Additional research on age specific effects of selenium toxicity does not appear necessary at present.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

The American Health Foundation is involved in on-going research to develop new organoselenium chemopreventive agents for cancer having an increased therapeutic ratio compared with some of the historical selenium compounds, such as selenite. Additional federally sponsored research that was reported in the CRIS/USDA (2001) and CRISP (2001) databases is shown in Table 3-8.

Table 3-8. On-going Studies on Selenium Health Effects

Investigator	Institute	Research Area	Reference
Alberts, DS	University of Arizona	Phase III trials of chemopreventive agents on colon carcinogenesis	CRISP 2001
Cohen, HJ	Stanford University	Relationship of the synthesis and secretion of an extracellular selenium dependent glutathione peroxidase to changes in renal function	CRISP 2001
Combs, GF	Cornell University	Metabolic events at extremes of selenium intake; characterization of antioxidant status of a large cohort of free-living Americans	CRIS/UDSA 2001
Beran, M	Vyzkumny Ustav Potravinarsky	Evaluation of combined supplementation with selenium and iodine on levels of selenium-dependent enzymes, thyroidal hormones and other biochemical parameters.	CRIS/UDSA 2001
Berry, MJ	Brigham and Women's Hospital	Mechanism of selenoprotein synthesis in eukaryotes	CRISP 2001
Berry, MJ	Brigham and Women's Hospital	Selenoprotein P function and regulation of expression	CRISP 2001
Block, E	Roswell Park Memorial Institute	Identify selenium compounds from high-selenium garlic	CRISP 2001
Bosland, MC	New York University School of Medicine	Preclinical prostate cancer chemoprevention studies	CRISP 2001
Burk, RF	Vanderbilt University	Selenium supplementation of patients with cirrhosis	CRISP 2001
Burk, RF	Vanderbilt University	Selenoprotein-P structure, function and activity	CRISP 2001
Cassano, PA	Cornell University	Nutritional influences on lung disease	CRIS/UDSA 2001
Coltman, CA	CTRC Research Foundation	Chemoprevention of prostate cancer	CRISP 2001
Combs, GF	Cornell University	Kinetics of organic and inorganic selenium during dietary supplementation	CRIS/UDSA 2001
Davis, CD	Agricultural Research Service	Role of selenium in cancer susceptibility	CRIS/UDSA 2001

Table 3-8. On-going Studies on Selenium Health Effects (*continued*)

Investigator	Institute	Research Area	Reference
Diamond, AM	University of Illinois	Mechanism by which selenium protects against mutagenesis	CRISP 2001
Driscoll, DM	Cleveland Clinic Foundation	Mechanism of selenoperoxidase biosynthesis	CRISP 2001
El-Bayoumy, KE	American Health Foundation	Chemoprevention of oral cancer: model studies	CRISP 2001
El-Bayoumy, KE	American Health Foundation	Chemoprevention of lung cancer: model studies	CRISP 2001
El-Bayoumy, KE	American Health Foundation	Chemoprevention of mammary cancer by organoselenium	CRISP 2001
Fiala, E	American Health Foundation	Organoselenium compounds as modifiers of carcinogenesis	CRISP 2001
Ganther, H	Roswell Park Memorial Institute	Selenium metabolism and anti-carcinogenic action	CRISP 2001
Ganther, H	University of Wisconsin	Organoselenium compounds biosynthesis and function	CRIS/UDSA 2001
Gesteland, RF	University of Utah	Genetic analysis of synthesis of selenium containing proteins	CRISP 2001
Gladyshev, VN	University of Nebraska	Identity of terminator and selenocysteine UGA codons	CRISP 2001
Gladyshev, VN	University of Nebraska	Biochemistry and molecular biology of selenium containing enzymes	CRIS/UDSA 2001
Glauert, HP	University of Kentucky	Effect of dietary antioxidants on hepatic NF-KB activation	CRIS/UDSA 2001
Gottschall, EB	National Jewish Medical and Research Center	Randomized, placebo-controlled, double blind trial of asbestos-exposed workers using high selenium yeast supplementation	CRISP 2001
Guttenplan, JB	New York University	Antimutagenesis by lycopene and selenium in rodents	CRISP 2001
Ip, C	Roswell Park Memorial Institute	Mammary cancer prevention by novel selenium compounds; selenium metabolism and cancer prevention	CRISP 2001
James, LF	Agricultural Research Service	Livestock poisoning from *Astragalus* and *Oxytropis* species	CRIS/UDSA 2001

Table 3-8. On-going Studies on Selenium Health Effects (*continued*)

Investigator	Institute	Research Area	Reference
Kim, J	University of Texas MD Anderson Cancer Center	Feasibility study of L-selenomethionine in prevention of prostate cancer	CRISP 2001
Kolonel, LN	University of Hawaii at Manoa	Epidemiologic studies of diet and cancer in Hawaii	CRISP 2001
Kolonel, LN	University of Hawaii at Manoa	Biomarkers of prostate cancer risk in a multi ethnic cohort	CRISP 2001
Koutnik, V	University of Brno	Selenium in food chains and its impact on human health	CRIS/UDSA 2001
Lei, X	Cornell University	Antioxidative role of glutathione peroxidase in transgenic mice	CRISP 2001
Levander, OA	Agricultural Research Service	Role of vitamin E and selenium in human health promotion	CRIS/UDSA 2001
Levander, OA	University of Maryland	Kinetics of organic and inorganic selenium during dietary supplementation	CRIS/UDSA 2001
Marshall, JR	University of Arizona	Phase III trial of selenium for prostate cancer prevention	CRISP 2001
May, JM	Vanderbilt University	Antioxidant interactions of selenium and vitamins C and E	CRISP 2001
Medina, D	Roswell Park Memorial Institute	Selenoproteins in rat mammary tumorigenesis	CRISP 2001
Nomura, AM	Kuakini Medical Center	Cancer epidemiology of migrant Japanese in Hawaii	CRISP 2001
Pence, BC	Texas Technical University Health Sciences Center	Induction by selenium of the antioxidant and the prooxidant, apoptotic pathways in cultured cells	CRISP 2001
Powis, G	University of Arizona	Thioredoxin reductases and cancer	CRISP 2001
Prolla, TA	University of Wisconsin	Role of dietary selenium in intestinal tumorigenesis	CRISP 2001
Rao, L	University of Wisconsin	Genetic characterization of the selenoenzyme phospholipid -hydroperoxide glutathione peroxidase	CRISP 2001
Reddy, BS	American Health Foundation	Chemoprevention of cancer by organoselenium compounds	CRISP 2001

Table 3-8. On-going Studies on Selenium Health Effects (*continued*)

Investigator	Institute	Research Area	Reference
Reddy, CC	Pennsylvania State University	Antioxidant effects on prostaglandin metabolism, lipid peroxidation and Immunologic defense	CRIS/UDSA 2001
Roberts, JC	University of Utah	Preparation and preliminary studies of selenazoidine carboxylic acids as novel selenium delivery agents	CRISP 2001
Roy, M	New York University	Selenium supplementation and immunocompetence in the elderly	CRIS/UDSA 2001
Smith, AM	Ohio State University	Influence of gender and life cycle on selenium requirements and metabolism	CRIS/UDSA 2001
Sunde, RA	University of Missouri	New essential roles for selenium; regulatory elements of selenium-dependent peroxidases; regulatory elements of the rat glutathione peroxidase gene	CRIS/UDSA 2001
Taylor, EW	University of Georgia	Selenoproteins, NF-KB, and HIV disease in drug users	CRISP 2001
Thompson, I	University of Texas Health Science Center San Antonio	Biomarkers of risk for prostate cancer	CRISP 2001
Thompson, H	Roswell Park Memorial Institute	Mechanisms of selenium anticancer and toxic activities	CRISP 2001
Thompson, H	Roswell Park Memorial Institute	Six month trial of selenium as a chemopreventive agent for lung cancer.	CRISP 2001
Veillon, C	Agricultural Research Service	Metabolism, function, and interactions of selenium using stable isotopes	CRIS/UDSA 2001
Weiss, SL	University of Missouri	Molecular basis for selenium regulation of glutathione peroxidase mRNA	CRIS/UDSA 2001
Whanger, PD	Oregon State University	The metabolic function of selenoprotein W	CRISP 2001

Table 3-8. On-going Studies on Selenium Health Effects (*continued*)

Investigator	Institute	Research Area	Reference
Whanger, P	Oregon State University	Role of selenium and vitamin E in scour and immunity of newborn calves; influence of pregnancy on selenium metabolism in women of low selenium status; metabolic relationship between selenium and myopathy	CRIS/UDSA 2001
Yu, MC	University of Southern California	Singapore cohort study of diet and cancer	CRISP 2001

NCI = National Cancer Institute; NIH = National Institutes of Health